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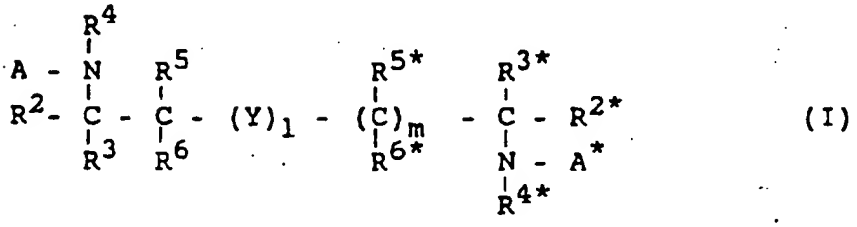
Inhibitors of retroviral proteases

The present invention concerns compounds of formula I



(I)

wherein

A, Y, R^2, R^3, R^4, R^5, R^6, l, m and the corresponding radicals indicated by * are defined as stated in the description, a process for their preparation and their use for the inhibition of retroviral proteases.

INHIBITORS OF RETROVIRAL PROTEASES

The present invention concerns substances which inhibit the action of retroviral proteases, processes for their preparation, their use and drugs containing them.

The etiological cause of acquired immune deficiency syndrome (AIDS) is the so-called human immunodeficiency virus (HIV) (F. Barre-Sinoussi, et al., Science 220, (1983), 868-870; R. C. Gallo, et al., Science 224, (1984), 500-

502; R. C. Gallo and L. Montagnier, Scient. Am. 259(4), (1988), 40-48). HIV is a retrovirus and belongs to the group of lentiviruses (M. A. Gonda, F. Wong-Staal and R. C. Gallo, Science 227 (1985), 173; P. Songio, et al., Cell, 42, (1985), 369).

The AIDS epidemic has meanwhile more or less spread over almost all countries. About 160,000 cases have been reported to the World Health Organization (WHO) from 149 countries. The WHO estimates the actual number to be about 500,000 cases; the number of infected persons to be about 5-10 million (J. M. Mann at the 5th International Conference on Aids, Montreal, 4-9 June 1989, see e.g. C&EN, June 26 (1989), 7-16).

The only substance thus far licensed for the indication of AIDS, zidovudine (AZT), is able in many cases to prolong the life of patients, but has serious toxic side effects which in many cases require discontinuation of the therapy. Also, the first strains of HIV that show a distinctly lesser sensitivity to AZT, and thus indicate the danger of a resistance, have already been discovered (C&EN see above). Further points of departure in HIV therapy are therefore urgently necessary.

Analogous to proteins of other viruses HIV proteins are first translated as long precursors polyproteins gag, pol and env (C. Dickson, et al. in RNA Tumor Viruses (editors: R. Weiss, N. Teich, H. Varmus and J. Coffin) 2nd Ed., revised, pages 513-648, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY), and only thereafter proteolytically processed to the structure proteins (p17 (MA), p24 (CA), p7 (NC) and p6), the enzymes (protease (PR), reverse transcriptase (RT) and integrase (IN)), and the sheath proteins (gp120 (SU) and gp41 (TM)) (nomenclature: J. Leis, et al., J. Virol., 62 (1988), (1808-1809). It is assumed that the splitting of the gag and pol polyproteins is

effected by a virally coded protease. Mutations within the region coding the protease lead to non-infectious virus particles (N. E. Kohl et al., Proc. Natl. Acad. Sci. USA 85, (1988), 4686-4690).

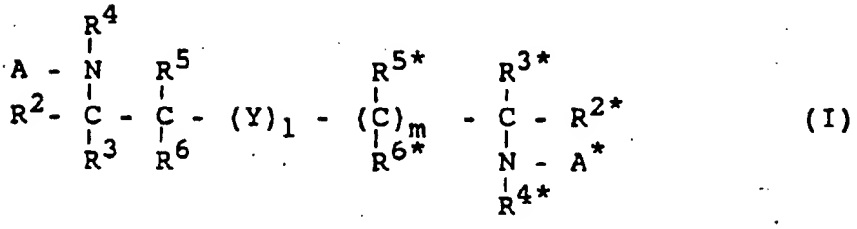
The HIV protease consists of 99 amino acids and obviously splits out by itself from the pol polyprotein through hydrolysis of the two phe-pro bonds in positions 68-69 and 167-168 (M. C. Graves, J. J. Lim, E. P. Heimer and R. A. Kramer, Proc. Natl. Acad. Sci. USA 85 (1988), 2449-2453; J. Hansen, S. Billich, T. Schulze, S. Sukrow and K. Mölling, EMBO J. 7 (1988), 1785-1791; E. P. Lillehoj, et al., J. Virology 62 (1988) 3053-3058; J. Schneider and S. B. H. Kent, Cell 54 (1988) 363-368).

Until now only few inhibitors of the HIV protease have been known in the literature. The first representative was pepstatin A with an IC_{50} value of about 0.5 mmol (I. Katoh, T. Yasunaga, Y. Ikawa and Y. Yoshinaka, Nature, 329 (1987), 654-656). Meanwhile, several other moderately to highly effective inhibitors have been described (S. Billich, et al., J. Biol. Chem. 34 (1988), 17905-17098); M. Moore, et al., Biochem. Biophys. Res. Comm., 159, (1989), 420-425; A. D. Richards, R. Roberts, B. M. Dunn, M. C. Graves and J. Kay, FEBS Lett., 247, (1989), 113-117).

High doses of pepstatin A were able in biosynthesis to reduce the formation of the nucleoprotein p24 (v.d.Helm, L. Gürtler, J. Eberle an F. Deinhardt, FEBS Lett., 247, (1989), 349-352).

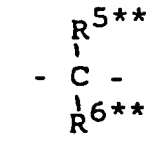
A new structure class has now been found that in the enzyme test inhibits the HIV protease highly effectively.

The present invention concerns compounds of formula I

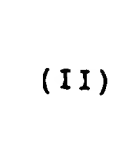


(I)

wherein Y stands for oxygen, sulfur a radical of formula II or a radical of formula III



(II)



(III)

l and m, independent of each other, are 0 or 1; A means a radical of formula IV and A* a radical of formula IV*

D - $(E)_n$ - (F_o) - $(G)_p$ - (IV)

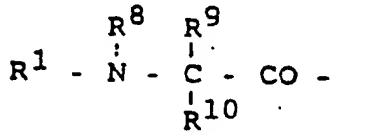
D* - $(E^*)_{n^*}$ - $(F^*)_{o^*}$ - $(G^*)_{p^*}$ - (IV*)

where E, E*, F, F*, G and G*, independent of one another, stand for a natural or an unnatural amino acid, azaamino acid or imino acid;

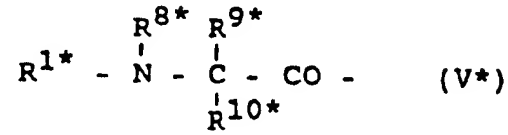
n, n*, o, o*, p and p*, independent of one another, mean 0 or 1;

D stands for R^1 or a radical of formulas V, VI or VII, and

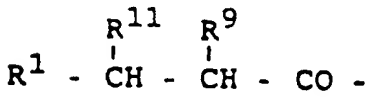
D* stands for R^{1*} or a radical of formulas V*, VI* or VII*



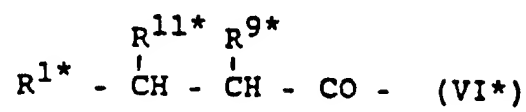
(V)



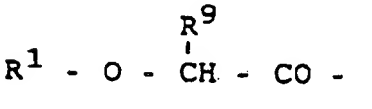
(V*)



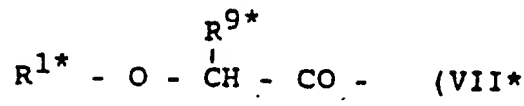
(VI)



(VI*)



(VII)



(VII*)

and wherein R^1 and R^{1*}, independent of each other, stand for

a_1)

- hydrogen
- carboxyl.
- (C_1-C_{18})-alkyl, which may be simply or doubly unsaturated and which may be substituted by up to 3 identical or different radicals from the series
- mercapto,
- hydroxy,
- (C_1-C_7)-Alkoxy
- Carbamoyl
- (C_1-C_8)-alkanoyloxy,
- carboxy,
- (C_1-C_7)-alkoxycarbonyl,
- F, Cl, Br, I,
- amino
- amidino, which if appropriate can be substituted by one, two or three (C_1-C_8)-alkyl radicals,
- guanidino, which if appropriate can be substituted by one or two benzyloxycarbonyl radicals or by one, two, three or four (C_1-C_8)-alkyl radicals,
- (C_1-C_7)- alkylamino,
- di-(C_1 -C_7)-alkylamino,
- (C_1-C_6)-alkoxycarbonylamino,
- (C_7-C_{15})-aralkoxycarbonyl,
- (C_7-C_{15})-aralkoxycarbonylamino,
- [illegible] (C_1-C_4)-alkoxy

- 9-fluorenylmethoxycarbonylamino,
- (C_1-C_6)-alkylsulfonyl,
- (C_1-C_6)-alkylsulfinyl,
- (C_1-C_6)-alkylthio,
- hydroxamino,
- hydroximino,
- sulfamoyl,
- sulfo,
- carboxamido,
- formyl,
- hydrazono,
- imino,
- a radical $CONR^{12}R^{13}$ or $CONR^{12*}R^{13*}$,
- by up to six hydroxy or
- by up to five (C_1-C_8)-alkanoxyloxy;
- mono-, bi- or tri-cyclic (C_3-C_{18})-cycloalkyl,
- (C_3-C_{18})-cycloalkyl-(C_1-C_6)-alkyl, the cycloalkyl part in each case being substituted if appropriate by one or two identical or different radicals from the series
- F, Cl, Br, I,
- carboxy,
- carbamoyl,
- carboxymethoxy,
- hydroxy,
- (C_1-C_7)-alkoxy,
- (C_1-C_7)-alkyl,

- (C_1-C_7)-alkyloxycarbonyl,
- amino,
- (C_1-C_6)-alkylamino-(C_1-C_6)-alkyl,
- di-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl,
- amidino,
- hydroxamino,
- hydroximino,
- hydrazono,
- imino,
- guanidino,
- (C_1-C_6)-alkoxysulfonyl,
- (C_1-C_6)-alkoxysulfinyl,
- (C_1-C_6)-alkoxycarbonylamino
- (C_6-C_{12})-aryl-(C_1-C_4)-alkoxycarbonylamino,
- (C_1-C_7)-alkylamino,
- di-(C_1-C_7)-alkylamino and
- trifluoromethyl;
- (C_6-C_{14})-aryl,
- (C_6-C_{14})-aryl-(C_1-C_6)-alkyl,
- (C_6-C_{14})-aryloxy-(C_1-C_6)-alkyl or
- (C_6-C_{14})-aryl-(C_3-C_8)-cycloalkyl, wherein the aryl part in each case is substituted if appropriate by one, two or three identical or different radicals from the series
- F, Cl, Br, I,
- hydroxy,
- mono-, di- or tri-hydroxy-(C_1-C_4)-alkyl,

- trifluoromethyl,
- formyl,
- carboxamido,
- mono- or di-(C_1-C_4)-alkylaminocarbonyl,
- nitro,
- (C_1-C_7)-alkoxy,
- (C_1-C_7)-alkyl,
- (C_1-C_7)-alkoxycarbonyl,
- amino,
- (C_1-C_7)-alkylamino,
- di-(C_1-C_7)-alkylamino,
- carboxy,
- carboxymethoxy,
- amino-(C_1-C_7)-alkyl,
- (C_1-C_7)-alkylamino-(C_1-C_7)-alkyl,
- di-(C_1-C_7)-alkylamino-(C_1-C_7)-alkyl,
- (C_1-C_7)-alkoxycarbonylmethoxy,
- carbamoyl,
- sulfamoyl,
- (C_1-C_7)-alkoxysulfonyl,
- (C_1-C_8)-alkylsulfonyl,
- sulfo-(C_1-C_8)-alkyl and
- (C_1-C_6)-alkoxycarbonylamino;
- het,
- het-(C_1-C_6)-alkyl,
- het-(C_3-C_8)-cycloalkyl,

- het-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkyl,

- het-(C_3-C_8)-cycloalkoxy-(C_1-C_4)-alkyl,

- het-thio-(C_1-C_6)-alkyl,

- het-thio-(C_3-C_8)-cycloalkyl,

- het-thio-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkyl, where in each case het stands for the radical of a 5- to 7-member monocyclic or 8- to 10-member bicyclic ring system which can be benzanellated, aromatic, partly hydrogenated or completely hydrogenated, which can contain as heteroelements one, two, three or four different radicals from the group N, O, S. NO, SO, SO_2, which can be substituted with 1 to 6 hydroxy and which, if appropriate, is mono-, di- or tri-substituted as defined for (C_6-C_{14})-aryl under a_1) and/or with oxo,
or mean a radical $NR^{12}R^{13}$ or $NR^{12*}R^{13*}$,
or

a_2)

- a radical of formula VIII or VIII*

R^{1a}-W (VIII)

R^{1a*}-W* (VIII*)

wherein R^{1a} and R^{1a*} are defined like R^1 and R^{1*} under a_1) and W and W* stand for -CO-, -CS-, O-CO-, -SO_2-, -SO-, -S-, -$NHSO_2$-, -NHCO-, -CH(OH)-, N(OH)- or -CO-V- with V meaning a peptide with 1 to 10 amino acids;
or wherein R^1 and R^{1*}, independent of each other, together with R^{11} or R^{11*} and the atoms that carry them form monocyclic or bicyclic, saturated or partly unsaturated ring systems with 5-12 ring members which in addition to carbon can also contain 1 sulfur atom, which may be oxidized to sulfoxide or sulfone;

a_3)

- a glycosyl radical, preferably a glucofuranosyl or glucopyranosyl radical, which is derived from naturally occurring aldotetroses, aldopentoses, aldohexoses, ketopentoses, ketohexoses, desoxyaldoses, aminoaldoses and oligosaccharides as well as their stereoisomers;

R^2 and R^{2*}

are defined independent of each other like R^1 and R^{1*} under a_1) or a_2) or together with R^4 or R^{4*} and the atoms carrying them form mono- or bicyclic, saturated or partly unsaturated ring systems with 5 to 12 ring members, or together with R^3 or R^{3*} and the atoms carrying them form cyclic, saturated or partly unsaturated ring systems with 3 to 12 ring members;

R^3 and R^{3*}

independent of each other mean

- hydrogen or
- (C_1-C_3)-alkyl;

R^4 and R^{4*} mean

- hydrogen or
- (C_1-C_8)-alkyl;

R^5, R^{5*} and R^{5**}

independent of one another mean

- hydrogen,
- hydroxy,
- amino or
- carboxy, or

with R^6, R^{6*} or R^{6**} together with the carbon atoms carrying these, in each case independent of one another, form a keto group;

R^6, R^{6*} and R^{6**}

independent of one another mean

- hydrogen or

- (C_1-C_6)-alkyl or

in the case of l=0, R^6 and R^{6*} can possibly form a common bond;

R^7 means

- hydrogen,

- hydroxy or

- (C_1-C_6)-alkyl;

R^8 and R^{8*}

independent of each other mean

- hydrogen or

- (C_1-C_8)-alkyl, or together with R^9 or R^{9*} and the atoms carrying these form mono- or bicyclic, saturated or partly unsaturated ring systems with 5 to 12 ring members;

R^9 and R^{9*}

independent of each other are defined like R^1 or R^{1*} under a_1), stand for hydroxy or (C_1-C_4)-alkanoyloxy, or together with R^{10} or R^{10*} and the atoms carrying these form cyclic, saturated or partly unsaturated ring systems with 3 to 12 ring members;

or

together with R^{11} or R^{11*} and the atoms carrying these form a mono- or bicyclic, saturated or partly unsaturated ring system with 5-12 ring members, which in addition to carbon can also contain 1 sulfur atom, which possibly can be oxidized to sulfoxide or sulfone; or can contain 1 nitrogen atom, the ring system possibly being substituted by amino;

R^{10} and R^{10*}

independent of each other mean

- hydrogen or
- (C_1-C_6)-alkyl;

R^{11} and R^{11*}

independent of each other mean

- hydrogen,
- hydroxy,
- (C_1-C_4)-alkanoyloxy or
- (C_1-C_8)-alkyl;

R^{12}, R^{12*}, R^{13} and R^{13*}

independent of one another mean

- hydrogen,
- (C_1-C_8)-alkyl which can be substituted by
- amino,
- (C_1-C_4)-alkylamino,
- di-(C_1-C_4)-alkylamino,
- mercapto,
- carboxy,
- hydroxy or
- (C_1-C_4)-alkoxy,
- (C_3-C_7)-cycloalkyl,
- (C_1-C_4)-alkoxycarbonyl,
- (C_6-C_{14})-aryl, (C_6-C_{14})-aryl-(C_1-C_4)-alkoxycarbonyl which in the aryl part can be substituted as described for R^1 or R^{1*},
- het or
- het-(C_1-C_4)-alkyl, het being defined as described for R^1 or R^{1*},

or where R^{12} and R^{13} or R^{12*} and R^{13*} together with the nitrogen atoms carrying these form monocyclic or bicyclic, saturated, partly unsaturated or aromatic ring systems which in addition to carbon can also contain 1 or 2 nitrogen atoms, 1 sulfur atom or 1 oxygen atom as further ring members and which can be substituted by

$(C_1\text{-}C_4)$-alkyl,

where

in the compounds of formula I cited above, one or more amide groups (-CONH-) of the main chain can be replaced by $-CH_2NR^{14}-$, $-CH_2S-$, $-CH_2O-$, $-OCH_2-$, CH_2CH_2-, -CH=CH-(cis and trans), $-COCH_2-$, $-CH(OH)CH_2-$, $-CH_2SO-$, CH_2SO_2-, -COO-, $-P(O)(OR^{15})CH_2-$ and $-P(O)(OR^{15})NH-$, or also by an amide group with reversed polarity (-HCHO-);

wherein R^{14} and R^{15}

independent of each other stand for

- hydrogen or
- $(C_1\text{-}C_4)$-alkyl;

as well as their physiologically tolerated salts.

The nomenclature used in this description follows the general practice with amino acids; that is, the amino group stands to the left and the carboxyl groups to the right of each amino acid. The same applies correspondingly for azaamino acids and imino acids.

Natural or unnatural amino acids can, if chiral, be present in the D or L form. Preferred are α-amino acids. Cited as examples are:

Aad, Abu, γAbu, ABz, 2ABz, εAca, Ach, Acp, Adpd, Ahb, Aib, βAib, Ala, βAla, Ala, Alg, All, Ama, Amt, Ape, Apm, Apr, Arg, Asn, Asp, Asu, Aze, Azi, Bai, Bph, Can, Cit, Cys, $(Cys)_2$, Cyta, Daad, Dab, Dadd, Dap, Dapm, Dasu, Djen, Dpa,

Dtc, Fel, Gln, Glu, Gly, Guv, hAla, hArg, hCys, hGln, hGlu, His, hIle, hLeu, hLys, hMet, hPhe, hPro, hSer, hThr, hTrp, hTyr, Hyl, Hyp, 3Hyp, IIe, Ise, Iva, Kyn, Lant, Lcn, Leu, Lsg, Lys, ßLys, ΔLys, Met, Mim, Min, nArg, Nle, Nva, Oly, Orn, Pan, Pec, Pen, Phe, Phg, Pic, Pro, ΔPro, Pse, Pya, Pyr, Pza, Qin, Ros, Sar, Sec, Sem, Ser, Thi, ßThi, Thr, Thy, Thx, Tia, TIe, TIy, Trp, Trta, Tyr, Val, Nal, Tbg, Npg, Chg, Thia (see for example Houben-Weyl, Methods of Organic Chemistry, vol XV/1 and 2, Stuttgart, 1974).

Azaamino acids are derived from natural or unnatural amino acids, the central building block -CHR- or CH_2- being replaced by -NR- or -NH-.

An imino acid is generally understood to be a natural or unnatural amino acid the amino group of which is monosubstituted. Mentioned in particular in this connection are the compounds that are substituted by $(C_1$-$C_8)$-alkyl, which in turn may be substituted as described on pages 4/5 [Note: page references herein are to the original document]. In addition, heterocycles from the following group also come into consideration:

pyrrolidine-2-carboxylic acid;

piperidine-2-carboxylic acid;

1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid;

decahydroisoquinoline-3-carboxylic acid;

octahydroquinoline-2-carboxylic acid;

decahydroquinoline-2-carboxylic acid;

octahydrocyclopenta[b]pyrrole-2-carboxylic acid;

2-aza-bicyclo[2.2.2]octo-3-carboxylic acid;

2-azabicyclo[2.2.1]heptane-3-carboxylic acid;

2-azabicyclo[3.1.0]hexane-3-carboxylic acid;

2-azaspiro[4.4]nonane-3-carboxylic acid;

2-azaspiro[4.5]decane-3-carboxylic acid;

spiro[(bicyclo[2.2.1]-heptane)-2,3-pyrrolidine-5-carboxylic acid];

spiro[(bicyclo[2.2.2]octane)-2,3-pyrrolidine-5-carboxylic acid];

2-azatricyclo[4.3.0.$1^{6,9}$]decane-3-carboxylic acid;

decahydrocyclohepta[b]pyrrole-2-carboxylic acid;

decahydrocycloocta[b]pyrrole-2-carboxylic acid;

octahydrocyclopenta[c]pyrrole-2-carboxylic acid;

octahydroisoindole-1-carboxylic acid;

2,3,3a,4,6a-hexahydrocyclopenta[b]pyrrole-2-carboxylic acid;

2,3,3a,4,5,7a-hexahydroindole-2-carboxylic acid;

tetrahydrothiazole-4-carboxylic acid;

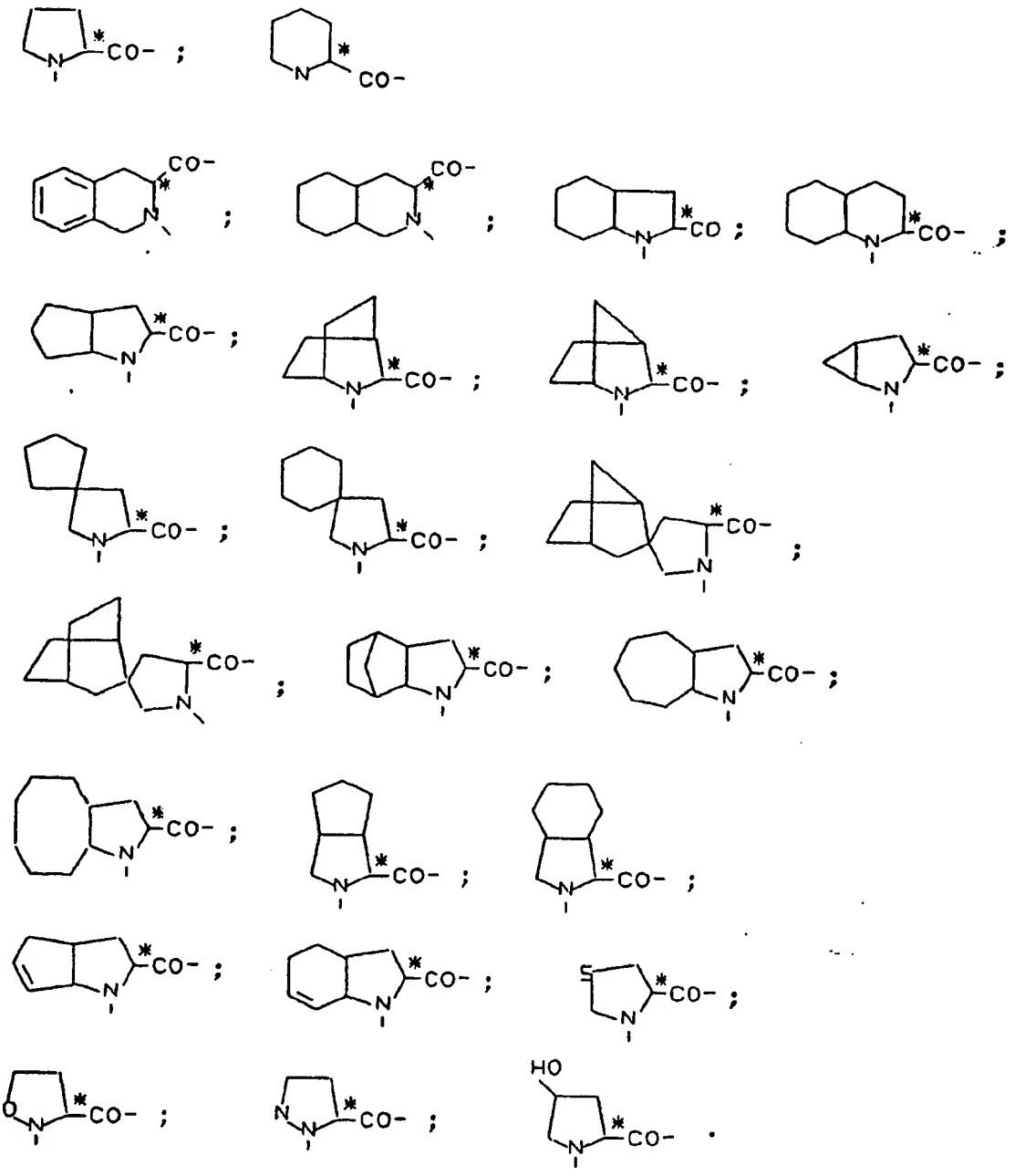
isoxazolidine-3-carboxylic acid;

pyrazolidine-3-carboxylic acid;

hydroxyproline-2-carboxylic acid, all of which may possibly be substituted:

Glycol radicals as described above are derived in particular from natural D or L monosaccharides occurring in microorganisms, plants, animals or humans, e.g. ribose (Rib), arabinose (Ara), xylose (Xyl), lyxose (Lyx), allose (All), altrose (Alt), glucose (Glc), mannose (Man), gulose (Gul), idose (Ido), galactose (Gal), talose (Tal), erythrose (Ery), Threose (Thr), psicose (Psi), fructose (Fru), sorbose (Sor), tagatose (Tag), xylulose (Xyu), fucose (Fuc), rhamnose (Rha), olivose (Oli), oliose (Olo), mycarose (Myc), rhodosamine (RN), N-acetyl-glucosamine (GlcNAc), N-acetyl-galactosamine (GalNAc), N-acetyl-mannosamine (ManNAc) or disaccharides such as maltose (Mal), lactose (Lac), cellobiose (Cel), gentibiose (Gen), N-acetyl-lactosamine (LacNAc), chitobiose (Chit), ß-galactopyranosyl-(1,3)-N-acetylgalactosamine and ß-galactopyranosyl-(1,3)- or -(1,4)-N-acetyl-glucosamine, as well as their synthetic derivatives

such as 2-desoxy-, 2-amino-, 2-acetamino- or 2-halogeno-, preferably bromo and iodo sugar.



The chirality centers in the compounds of formula (I) can exhibit the R, S or R,S configuration.

Alkyl can be straight-chain or branched. This applies correspondingly to radicals derived therefrom, such as alkoxy, alkylthio, alkylamino, dialkylamino, alkanoyl and aralkyl.

Cycloalkyl also means alkyl-substituted radicals such as 4-methoxycyclohexyl or 2,3-dimethylcyclopentyl.

By bicycloalkyl or tricycloalkyl is meant an isocyclic aliphatic, non-aromatic radical which can possibly contain non-symmetrically distributed double bonds and can possibly be substituted with open-chain aliphatic lateral chains. The two or three rings as components of such radicals are condensed or spiro-joined and are joined via a ring C atom or a lateral chain C atom. Examples of these radicals are bornyl-, norbornyl-, pinanyl-, norpinanyl-, caranyl-, norcaranyl-, thujanyl-, adamantyl-, bicyclo(3.3.0)octyl-, bicyclo(4.4.0)decyl-, bicyclo(1.1.0)butyl-, spiro(3.3)heptyl substituents.

If the cycles cited carry more than one substitute, these can stand either cis or trans to one another.

$(C_6$-$C_{14})$-aryl is, for example, phenyl, naphthyl, biphenylyl or fluorenyl; preferred are phenyl and naphthyl. The same applied correspondingly to radicals derived therefrom, e. g. aryloxy, aroyl, aralkyl and aralkoxy. By aralkyl is meant an unsubstituted or substituted $(C_6$-$C_{14})$-aryl radical joined to $(C_1$-$C_6)$-aryl such as benzyl, 1- and 2-naphthylmethyl, although aralky would not be limited to the radicals cited.

Het radicals in the sense of the definition above are pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, tetrazolyl, pyridyl, pyrazinyl, pyrimidinyl, indolyl, isoindolyl, indazolyl, phthalazinyl, quinolyl, isoquinolyl, quinoxalinyl, quinazolinyl, cinnolinyl,

ß-carbolinyl, or a benzanellated, cyclopenta-, cyclohexa- or cycloheptannelated derivative of these radicals.

These heterocycles can be substituted and partly or completely saturated at a nitrogen atom by oxides; (C_1-C_7)-alkyl e. g. methyl or tehyl; phenyl; phenyl-(C_1-C_4)-alkyl e. g. benzyl; and/or at one or more carbon atoms by (C_1-C_4)-alkyl e g. methyl; phenyl; phenyl-(C_1-C_4)-alkyl; halogen; hydroxy; (C_1-C_4)-alkoxy, e. g. methoxy; phenyl-(C_1-C_4)-alkoxy, e. g. benzyloxy; or oxo.

Such radicals are, for example, 2- or 3-pyrrolyl; phenyl-pyrrolyl, e. g. 4- or 5-phenyl-2-pyrrolyl; 2-furyl; 2-thienyl; 4-imidazolyl; methyl-imidazolyl, e. g. 1-methyl-2-, -4- or -5-imidazolyl; 1,3-thiazol-2-yl; 2-, 3- or 4-pyridyl; 1-oxido-2-, -3- or -4-pyridino; 2-pyrazinyl; 2-, 4- or 5-pyrimidinyl; 2-, 3- or 5-indolyl; substituted 2-indoyl, e. g. 1-methyl-, 5-methyl-, 5-benzyloxy-, 5-chloro- or 4,5-dimethyl-2-indolyl; 1-benzyl-2- or -3-indolyl; 4,5,6,7-tetrahydro-2-indolyl; cyclohepta[b]-5-pyrrolyl; 2-, 3- or 4-quinolyl; 1-, 3- or 4-isoquinolyl; 1-oxo-1,2-dihydro-3-isoquinolyl; 2-quinoxalinyl; 2-benzofuranyl; 2-benzoxazolyl; benzothiazolyl; benz[e]indole-2-yl or ß-carboline-3-yl.

Partly hydrogenated or completely hydrogenated heterocyclic rings are, for example, dihydropyridinyl; pyrrolidinyl, e. g. 2-, 3- or 4-N-methyl-pyrollidinyl; piperazinyl; morpholino; thiomorpholino, tetrahydrothiophenyl; benzodioxolanyl.

Halogen stands for fluorine, chlorine, bromine or iodine, especially for fluorine or chlorine.

By salts of compounds of formula (I) are meant in particularly pharmaceutically usable or non-toxic salts.

Such salts are formed, for example, from compounds of formula (I), which contain acid groups such as carboxy, with alkaline or alkaline earth metals such as Na, K, Mg and Ca, as well as with physiologically tolerated organic amines such as triethylamine and tris-(2-hydroxy-ethyl)-amine.

Compounds of formula (I) containing basic groups, e. g. an amino group or a guanidino group, form salts with inorganic acids such as hydrochloric acid, sulfuric acid or phosphoric acid and with organic carboxylic or sulfonic acids such as acetic acid, citric acid, benzoic acid, maleic acid, fumaric acid, tartaric acid and toluene-p-sulfonic acid.

Preferred are compounds of formula I wherein the radicals and symbols with and without asterisk are in each case identical.

Likewise preferred are compounds of formula I that are C_2-symmetrical.

In addition, preferred are compounds of formula I in which

Y stands for a radical of formula II or a radical of formula III;

l, m, A, A*, D, D*, n, n*, o, o*, p and p* are defined as above;

E, E*, F, F*, G and G*, independent of one another, stand for a natural or unnatural α-amino acid or α-imino acid;

R^1 and R^{1*}

independent of each other stand for

a_1) - hydrogen,

- carboxyl,

- (C_1-C_{16})-alkyl, which may be simply saturated and which may be substituted by up to 2 identical or different radicals from the series

- hydroxy,

- (C_1-C_4)-alkoxy,

- carbamoyl,

- (C_1-C_8)-alkanoyloxy,
- carboxy,
- (C_1-C_4)-alkoxycarbonyl,
- F,
- amino,
- (C_1-C_7)-alkylamino,
- di-(C_1-C_7)-alkylamino,
- (C_1-C_6)-alkoxycarbonylamino,
- benzyloxycarbonyl,
- benzyloxycarbonylamino,
- 9-Fluorenylmethoxycarbonylamino,
- (C_1-C_4)-alkylsulfonyl,
- a radical $CONR^{12}R^{13}$ or $CONR^{12*}R^{13*}$,
- by up to six hydroxy or
- by up to four (C_1-C_8)-alkanoyloxy;
- mono- or bicyclic (C_3-C_{12})-cycloalkyl,
- (C_3-C_{12})-cycloalkyl-(C_1-C_6)-alkyl where in each case the cycloalkyl part is substituted by one or two identical or different radicals from the series
- F,
- carboxy,
- hydroxy,
- (C_1-C_7)-alkoxy,
- (C_1-C_4)-alkyl,
- (C_1-C_4)-alkyloxycarbonyl,
- amino,
- (C_1-C_6)-alkoxycarbonylamino,

- benzyloxycarbonylamino,
- (C_1-C_4)-alkylamino and
- di-(C_1-C_4)-alkylamino;
- (C_6-C_{10})-aryl,
- (C_6-C_{10})-aryloxy-(C_1-C_6)-alkyl or
- (C_6-C_{10})-aryl-(C_1-C_6)-alkyl, wherein the alkyl part in each case is possibly substituted by one, two or three identical or different radicals from the series
- F, Cl, Br,
- hydroxy,
- hydroxy-(C_1-C_4)-alkyl,
- carboxamido,
- mono- or di-(C_1-C_4)-alkylaminocarbonyl,
- (C_1-C_4)-alkoxy,
- (C_1-C_4)-alkyl,
- (C_1-C_4)-alkoxycarbonyl,
- amino,
- (C_1-C_4)-alkylamino,
- di-(C_1-C_4)-alkylamino,
- carboxy,
- carbamoyl,
- (C_1-C_4)-alkoxycarbonylamino;
- het,
- het-(C_1-C_6)-alkyl,
- het-(C_5-C_6)-cycloalkyl,
- het-thio-(C_1-C_4)-alkyl,

- het-thio-(C_5-C_6)-cycloalkyl,

where het in each case stands for a 5- to 6-member monocyclic or 8- to 10-member bicyclic ring system which can be aromatic, partly hydrogenated or completely hydrogenated, which can contain as heteroelements one, two, three of four different radicals from the group N, O, S, NO, SO, SO_2, which can be substituted with 1 to 4 hydroxy and which can possibly be mono- or di-substituted as defined for (C_6-C_{10})-aryl under a_1) and/or with oxo,

or means a radical $NR^{12}R^{13}$ or $NR^{12*}R^{13*}$ or,

a_2) - a radical of formula VIII or VIII*

R^{1a} - W (VIII)

R^{1a*} - W* (VIII*)

wherein R^{1a} and R^{1a*} are defined like R^1 an R^{1*} under a_1) and W or W* stand for -CO-, -O-CO-, $-SO_2-$, -SO-, -S-, -NHCO- or -CH(OH)-;

or wherein R^1 and R^{1*} independent of each other together with R^{11} or R^{11*} and the atoms carrying these form monocyclic, saturated or partly unsaturated ring systems with 5-8 ring members, which in addition to carbon also can contain 1 sulfur atom, which can possibly be oxidized to sulfoxide or sulfone;

a_3) - a glycol radical that is defined as above;

R^2 and R^{2*}

independent of each other mean

b_1) hydrogen,

- carboxy,

- (C_1-C_{10})-alkyl which is possibly simply or doubly unsaturated and which is possibly substituted by up to 3 identical or different radicals from the series

-hydroxy,

- (C_1-C_7)-alkoxy,
- (C_1-C_7)-alkylthio,
- (C_1-C_7)-alkylsulfinyl,
- (C_1-C_7)-alkylsulfonyl,
- (C_1-C_7)-alkanoyloxy,
- carboxy,
- (C_1-C_7)-alkoxycarbonyl,
- Cl, Br,
- amino,
- amidino,
- guanidino,
- N,N'-di-(benzyloxycarbonyl)-guanidino,
- Carbamoyl,
- (C_7-C_{15})-aralkoxycarbonyl,
- (C_1-C_5)-alkoxycarbonylamino
- (C_1-C_{15})-aralkoxycarbonylamino or
- 9-fluorenylmethoxycarbonylamino;
- (C_3-C_{12})-cycloalkyl,
- (C_3-C_{12})-cycloalkyl-(C_1-C_3)-alkyl,
- (C_6-C_{14})-aryl,
- (C_6-C_{14})-aryl-(C_1-C_3)-alkyl, the aryl part in each case possibly being substituted by one, two or three identical or different radicals from the series
- F, Cl, Br, I,
- hydroxy,
- (C_1-C_7)-alkoxy,

- (C_1-C_7)-alkyl,

- (C_1-C_7)-alkoxycarbonyl,

- amino and

- trifluoromethyl; or

- het-(C_1-C_6)-alkyl, het standing for the radical of a 5- or 6-member monocyclic or 9- to 10-member bicyclic, possibly partly or completely hydrogenated heteroaromatic compound with at least 1 C atom, 1-4 N atoms and/or 1-2 S atoms and/or 1-2 O atoms as ring members, which is possibly mono- or di-substituted as described on pages 6/7 for the aryl part; or

b_2) together with R^4 or R^{4*} and the atoms carrying these form pyrrolidine or piperidine, which in each case can also be annelated with cyclopentyl, cyclohexyl or phenyl, [TEXT MISSING] with the atoms carrying these form cyclic, saturated or partly unsaturated ring systems with 3-8 ring members;

R^3 and R^{3*}

independent of each other mean

- hydrogen,

- methyl or

- ethyl;

R^4 and R^{4*}

independent of each other mean

- hydrogen,

- (C_1-C_4)-alkyl;

R^5, R^{5*} and R^{5**}

independent of each other are as defined on page 9;

R^6, R^{6*} and R^{6**}

independent of one another mean

- hydrogen,

- (C_1-C_4)-alkyl;

R^7

means

- hydrogen,

- hydroxy or

- $C_1-C_4)$-alkyl;

R^8 and R^{8*}

independent of each other mean

- hydrogen,

- (C_1-C_8)-alkyl or together with R^9 or R^{9*} and the atoms carrying these form pyrrolidine or piperidine, which in each case can additionally be annelated with cyclopentyl, cyclohexyl or phenyl;

R^9 and R^{9*}

independent of each other are defined like R^2 or R^{2*} under b_1), or mean (C_1-C_8)-alkyl, or

together with R^{10} or R^{10*} and the atoms carrying these form a mono- or bicyclic, saturated or partly unsaturated ring system with 5-12 ring members;

or

together with R^{11} or R^{11*} and the atoms carrying these form a mono- or bicyclic, saturated or partly unsaturated ring system with 5-12 ring elements, which in addition to carbon can also contain 1 sulfur atom which can possibly be oxidized to sulfoxide or sulfone;

R^{10} and R^{10*}

independent of each other mean

- hydrogen or

- (C_1-C_4)-alkyl;

R^{11} and R^{11*}

independent of each other mean

- hydrogen,
- hydroxy,
- (C_1-C_4)-alkanoyloxy or
- (C_1-C_4)-alkyl;

R^{12}, R^{12*}, R^{13} and R^{13*}

independent of one another mean

- hydrogen,
- (C_1-C_8)-alkyl, which can be substituted by
- amino,
- (C_1-C_4)-alkylamino,
- di-(C_1-C_4)-alkylamino,
- carboxy,
- hydroxy or
- (C_1-C_4)-alkoxy,
- (C_1-C_4)-alkoxycarbonyl,
- (C_6-C_{10})-aryl, which can be substituted as described for R^1 or R^{1*},
- (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonyl,
- het or
- het-(C_1-C_4)-alkyl, het being defined as described for R^1 or R^{1*},

it being possible in the aforementioned compounds of formula I for one or more amide groups (-CONH-) of the main chain to be replaced by a group consisting of $-CH_2-NR^{14}-$, $-CH_2-O-$, $-OCH_2-$, $-CH_2-CH_2-$, $-COCH_2-$, $-CH(OH)CH_2-$, -COO- or by an amide group of reverse polarity (-NHCO-);

R^{14} stands for

- hydrogen or
- (C_1-C_4)-alkyl;

as well as their physiologically tolerated salts.

Particularly preferred are compounds of formula I in which

Y stands for a radical of formula II or a radical of formula III;

l, m, A, A*, D, D*, n, n*, o, o* are defined as above, p and p* stand for 1;

R^1 and R^{1*}

independent of each other stand for

- hydrogen,
- carboxyl,
- (C_1-C_{10})-alkyl,
- (C_3-C_8)-cycloalkyl,
- (C_3-C_8)-cycloalkyl-(C_1-C_{10})-alkyl,
- phenyl-(C_1-C_8)-alkyl, which in the phenyl part can be substituted as described on pages 19/20,
- possibly protected mono- or di-amino-(C_1-C_{12})-alkyl or amino-(C_6-C_{10})-aryl-(C_1-C_4)- alkyl or amino-(C_3-C_{10})-cycloalkyl-(C_1-C_4)-alkyl, such as -2-amino-3-phenyl-propyl,
- mono-, di-, tris-, tetra-, penta- or hexahydroxy-(C_1-C_{10})-alkyl or -alkanoyl,
- (C_1-C_4)-alkoxy-(C_1-C_{10})-alkyl,
- (C_1-C_4)-alkoxycarbonyl-(C_1-C_{10})-alkyl,
- (C_1-C_{16})-alkylsulfonyl,
- (C_1-C_8)-alkylsulfinyl,
- mono-, di-, trihydroxy-(C_1-C_8)-alkylsufonyl,
- mono-, di-, trihydroxy-(C_1-C_8)-alkylsulfinyl,

- mono-, di-, tri- or tetra-(C_1-C_8)-alkanoyloxy-(C_1-C_{10})-alkyl,
- (C_1-C_4)-alkanoyl,
- possibly protected amino-(C_1-C_{11})-alkanoyl,
- di-(C_1-C_7)-alkylamino-(C_2-C_{11})-alkanoyl,
- (C_1-C_9)-cycloalkylcarbonyl,
- amino-substituted (C_3-C_9)-cycloalkylcarbonyl,
- amino-substituted (C_3-C_9)-cycloalkylsulfonyl,
- (C_6-C_{10})-aryl-(C_2-C_{11})-alkanoyl,
- (C_6-C_{10})-aryloxy-(C_2-C_{11})-alkanoyl,
- benzoyl, benzenesulfonyl or (C_6-C_{19})-aryl-(C_1-C_4)-alkylcarbonyl or sulfonyl possibly substituted by amino, halogen, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxy or (C_1-C_7)-alkoxycarbonyl,
- (C_1-C_{10})-alkoxycarbonyl,
- substituted (C_1-C_{10})-alkoxycarbonyl such as
- 2-(trimethylsilyl)ethoxycarbonly,
- 2,2,2-trichloroethoxycarbonyl or
- 1,1-dimethyl-2,2,2-trichloroethoxycarbonyl,
- (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl,
- (C_6-C_{10})-aryl-(C_1-C_8)-alkyl, (C_3-C_{10})-cycloalkyl-(C_1-C_8)-alkyl or (C_1-C_{10}) substituted by possibly protected amino and hydroxy, such as
- 2-amino-1-hydroxy-4-methyl-pentyl,
- 9-flourenylmethoxycarbonyl,
- ketohexosyl,
- ketopentosyl,
- deoxyhexoketosyl,
- dexoypentoketosyl,

- aldohexosyl,
- aldopentosyl,
- deoxyhexoaldosyl,
- deoxypentoaldosyl,
- 2-acetamido-2-dexoyhexosyl,
- lactosyl or
- maltosyl, in being possible for the joined sugar to be present in the pyranose or furanose form,
- het-(C_1-C_6)-alkyl,
- het-carbonyl or -sulfonyl,
- het-(C_1-C_6)-alkylcarbonyl or - sulfonyl,
- het-mercapto-(C_1-C_6)-alkylcarbonyl or -sulfonyl,

het in each case standing for

furyl, thienyl, benzothienyl, benzodioxolanyl, pyrrolyl, imidazolyl, isoxazolyl, thiazolyl, pyrazolyl, triazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolidyl, piperidyl, piperazinyl, morpholino, thiomorpholino, tetrahydrofuryl, tetrahydropyryl, tetrahydrothienyl, indolyl, quinolyl or isoquinolyl,

it also being possible for these to be substituted by one or two identical or different radicals from the group (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkoxycarbonylamino, hydroxy, amino, mono- or di-(C_1-C_4)-alkylamino and oxido;

R^2 and R^{2*}

independent of each other mean

- hydrogen,
- carboxyl,

- (C_1-C_8)-alkyl, which is possibly substituted by up to 2 identical or different radicals from the series

- hydroxy,

- (C_1-C_4)-alkoxy,

- (C_1-C_4)-alkylthio,

- (C_1-C_4)-alkylsulfinyl,

- (C_1-C_4)-alkylsulfonyl,

- (C_1-C_4)-alkanoyloxy,

- carboxy,

- (C_1-C_4)-alkoxycarbonyl,

- amino,

- amidino,

- guanidino,

- N,N'-di-(benzyloxycarbonyl)-guanidino,

- carbamoyl,

- (C_6-C_{10})-aryl-(C_1-C_3)-alkoxycarbonyl,

- (C_1-C_5)-alkoxycarbonylamino,

- (C_6-C_{10})-aryl-(C_1-C_3)-alkoxycarbonylamino, or

- (C_3-C_{10})-cycloalkyl,

- (C_3-C_{10})-cylcoalkyl-(C_1-C_3)-alkyl,

- (C_6-C_{10})-aryl,

- (C_6-C_{10})-aryl-(C_1-C_3)-alkyl, the aryl part possibly being substituted by one, two or three identical or different radicals from the series

- F, Cl, Br,

- hydroxy,

- (C_1-C_4)-alkoxy,

- (C_1-C_4)-alkyl,
- (C_1-C_4)-alkoxycarbonyl and
- amino, or
- het-(C_1-C_4)-alkyl, het being defines as for R^1 or R^{1*},

R^3 and R^{3*}

independent of each other mean

- hydrogen or
- methyl,

R^4 and R^{4*}

independent of each other mean

- hydrogen or
- methyl,

R^5, R^{5*} and R^{5**}

independent of one another mean

- hydrogen,
- hydroxy,
- amino or
- carboxy;

R^6, R^{6*} and R^{6**}

independent of one another mean

- hydrogen or
- methyl;

R^7 means

- hydrogen,
- hydroxy or
- methyl;

R^8 and R^{8*}

independent of each other mean

- hydrogen,

- methyl, ethyl or n-propyl, or together with R^9 or R^{9*} and the atoms carrying these form a 1,2,3,4-tetrahydroisoquinoline or a 2-azabicyclooctane skeleton;

R^9 and R^{9*}

independent of each other are defined like R^2 and R^{2*} on pages 27/28 or mean (C_1-C_8)-alkanoyloxy or

together with R^{10} or R^{10*} and the atoms carrying these form cyclic ring systems with 5 to 7 ring members;

or together with R^{11} or R^{11*} form a form a thiochroman system the sulfur atom of which can if appropriate be oxidized to sulfone;

R^{10} and R^{10*}

independent of each other mean

- hydrogen or

- methyl;

R^{11} and R^{11*} are defined as on page 24;

in the aforementioned compounds of formula I one or more amide groups (-CONH-) of the main chain can be replaced as defined n page 24;

R^{14} stands for

- hydrogen or

- methyl;

as well as their physiologically tolerated salts.

Also preferred are compounds of formula I in which

R^1 and R^{1*}

independent of each other stand for

a_1) - hydrogen,

- carboxyl,

- (C_1-C_{16})-alkylsulfonyl such as

- methylsulfonyl,

- tert.-butylsulfonyl,

- isopropylsulfonyl or

- hexadecylsulfonyl,

- (C_1-C_8)-alkylsulfinyl,

- (C_1-C_8)-mono-, di- or tri-hydroxyalkylsulfonyl, such as

- 2-hydroxyethylsulfonyl or

- 2-hydroxypropylsulfonyl,

- hydroxy-(C_1-C_{10})-alkanoyl, such as

- 2-hydroxypropionyl,

- 3-hydroxypropionyl,

- 3-hydroxybutyryl or

- 2-hydroxy-3-methylbutyryl,

- mono-, di-, tri- or tetra-hydroxy-(C_1-C_4)-alkyl, such as

- 1,2,3-trihydroxypropyl,

- 1,2-dihydroxyethyl or

- hydroxymethyl,

- (C_1-C_8)-alkanoyloxy-(C_1-C_{10}) alkyl, such as

- acetoxymethyl,

- 1,2-diacetoxyethyl,

- 1,2,3-triacetoxyethyl,

- (C_1-C_{14})-alkanoyl, such as

- n-decanoyl,

- formyl,
- acetyl,
- propionyl,
- pivaloyl,
- isovaleryl,
- isobutyryl or
- tetradecanoyl,
- amino-(C_1-C_{12})-alkanoyl, such as
- 3-amino-3,3-dimethyl-propionyl,
- 4-aminobutyryl,
- 5-aminopentanoyl,
- 6-aminohexanoyl or
- 12-aminododecanoyl,
- N-(C_1-C_4)-alkoxycarbonylamino-(C_1-C_8)-alkyl, such as
- 4-N-tert.-butoxycarbonylaminobutyryl,
- 5-N-tert.-butoxycarbonlyaminopentaloyl or
- 6-N-tert.-butoxycarbonylaminohexanoyl,
- di-(C_1-C_7)-alkylamino-(C_2-C_{11})-alkanoyl, such as
- dimethylaminoacetyl,
- (C_3-C_9)-cycloalkylcarbonyl, such as
- cyclopropylcarbonyl,
- cyclobutylcarbonyl,
- cyclopentylcarbonyl or
- cyclohexylcarbonyl,
- amino-(C_3-C_8)-cycloalkylcarbonyl, such as
- 2-aminocyclopropylcarbonyl,

- 3-aminocyclobutylcarbonyl,
- 3-aminocyclopentylcarbonyl or
- 4-aminocyclohexylcarbonyl,
- amino-(C_3-C_8)-cycloalkylsulfonyl, such as
- 3-aminocyclopentylsulfonyl or
- 4-aminocyclohexylsulfonyl,
- phenyl,
- (C_6-C_{10})-aryl-(C_2-C_{11})-alkanoyl, such as
- 1-naphthylacetyl,
- phenylpropranoyl or
- phenylbutanoyl,
- (C_6-C_{10})-aryloxy-(C_2-C_{11})-alkanoyl, such as
- 1-naphthyloxycarbonyl or
- phenyloxycarbonyl,
- benzoyl or benzenesylfonyl, possibly substituted by halogen, amino, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxy or (C_1-C_7)-alkoxycarbonyl, such as
- 4-chlorobenzoyl,
- 4-methylbenzoyl,
- 2-methoxycarbonylbenzoyl,
- 4-methoxybenzoyl,
- benzenesulfonyl or
- 4-methylphenylsulfonyl,
- benzylsulfonyl, benzylsulfinyl or benzylthio, possibly substituted by halogen, amino, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxy or (C_1-C_7)-alkoxycarbonyl, such as
- 4-chlorobenzylsulfonyl,

- benzylfulfinyl or
- 4-chlorobenzylthio,
- amino,
- (C_1-C_4)-alkoxycarbonylamino,
- (C_1-C_{12})-alkanoyl which is substituted by hydroxy, amino and possibly by phenyl or cyclohexyl, such as
- 2-amino-1-hydroxy-4-methyl-pentyl,
- possibly protected, amino-substituted (C_6-C_{10})-aryl- or (C_3-C_{10})-alkyl or (C_1-C_8)-alkyl, such as
- 2-amino-3-phenyl-propyl or
- N-tert.-butoxycarbonyl-2-amino-3-phenyl-propyl,
- (C_1-C_{10})-alkoxycarbonyl, such as
- methoxycarbonyl,
- ethoxycarbonyl,
- isobutoxycarbonyl or
- tert.-butoxycarbonyl,
- substituted (C_1-C_{10})-alkoxycarbonyl, such as
- 2-(trimethylsilyl)-ethoxycarbonyl,
- 2,2,2-trichloroethoxycarbonyl or
- 1,1-dimethyl-2,2,2-trichloroethoxycarbonyl,
- (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl, such as
- benzyloxycarbonyl,
- 1- or 2-naphthylmethoxycarbonyl or
- 9-fluorenylmethoxycarbonyl,
- 1-deoxyhexoketosyl or 1-deoxypentoketosyl, such as
- 1-deoxyfructos-1-yl, 1-deoxysorbos-1-yl or 1-deoxyribulos-1-yl

- hexosyl or pentosyl, such as
- mannosyl, glucosyl or galactosyl,
- xylosyl, ribosyl or arabinosyl,
- 6-deoxyhexosyl, such as
- rhamnosyl, fucosyl or deoxyglucosyl,
- amino sugar radicals, such as
- 2-amino-2-deoxyglucosyl,
- 2-acetamido-2-deoxyglucosyl,
- 2-amino-2-deoxygalactosyl or
- 2-acetamido-2-deoxygalactosyl,
- lactosyl,
- maltosyl,

it being possible for the joined sugar to be present in the pyranose or furanose form,

- het, such as
- 2-pyridyl,
- 4-pyridyl,
- 2-(N-oxidopyridyl) or
- 4-(N-oxidopyridyl),
- het-carbonyl or het-sulfonyl, such as
- piperidino-4-carbonyl,
- morpholino-4-carbonyl,
- pyrrolyl-2-carbonyl,
- pyridyl-3-carbonyl,
- quinolyl-2-carbonyl
- 4-tert.-butoxycarbonylamino-1-piperidylcarbonyl,

- 4-amino-1-piperidylcarbonyl,
- het-(C_1-C_6)-alkyl, such as
- 2-pyridyl-(C_1-C_6)-alkyl,
- 3-pyridyl-(C_1-C_6)-alkyl or
- 4-pyridyl-(C_1-C_6)-alkyl,
- het-(C_1-C_6)-alkanoyl or het-(C_1-C_6)-alkylsulfonyl, such as
- 2-pyridyl-(C_1-C_6)-alkanoyl,
- 3-pyridyl-(C_1-C_6)-alkanoyl,
- 4-pydidyl-(C_1-C_6)-alkanoyl,
- 2-pyridyl-(C_1-C_6)-alkylsulfonyl,
- 3-pyridyl-(C_1-C_6)-alkylsulfonyl or,
- 4-pyridyl-(C_1-C_6)-alkylsulfonyl,
- het-mercapto-(C_1-C_3)-alkylcarbonyl, such as
- 2-pyridylthioacetyl,

het standing in each case for

- pyrrolyl,
- imidazolyl,
- pyridyl,
- pyrimidyl,
- pyrrolidyl,
- piperidyl,
- morpholino,
- quinolyl or
- isoquinolyl,

and also possibly being substituted by one or two identical or different radicals from the group (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkoxycarbonylamino, hydroxy, amino, mono- or di-(C_1-C_4)-alkylamino;

R^2 and R^{2*}

independent of each other stand for

- hydrogen,
- carboxyl,
- methyl, ethyl, isopropyl, n-propyl, n-butyl, isobutyl, sec.-butyl, n-pentyl, n-hexyl,
- cyclohexyl,
- cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl,
- 4-methylcyclohexylmethyl,
- 1-decahydronaphthylmethyl, 2-decahydronaphthylmethyl,
- phenyl,
- benzyl,
- 2-phenylethyl,
- 1-naphthylmethyl, 2-naphthylmethyl,
- 2-methylbenzyl, 3- methylbenzyl, 4-methylbenzyl,
- 2,4,6-trimethylbenzyl,
- 4-tert.-butylbenzyl,
- 4-tert.-butoxybenzyl
- 4-hydroxybenzyl,
- 4-methoxybenzyl,
- 2,4-dimethoxybenzyl,
- 3,4-dihydroxybenzyl,
- 3,4-dimethoxybenzyl,

- (benzodioxolane-5-yl)methyl,
- 4-chlorobenzyl,
- hydroxymethyl,
- 1-hydroxyethyl,
- 4-pyridyl,
- 4-(N-oxidopyridyl),
- 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-(4-pyridyl)-ethyl,
- 2-thienylmethyl, 3- thienylmethyl,
- 2-(2-thienyl)ethyl, 2-(3-thienyl)ethyl,
- indole-2-yl-methyl, indole-3-yl-methyl,
- (1-methyl-imidazole-4-yl)methyl,
- imidazole-4-yl-methyl, imidazole-1-yl-methyl,
- 2-thiazolylmethyl,
- 3-pyrazolylmethyl,
- 4-pyrimidylmethyl,
- 2-benzo[b]thienylmethyl, 3-benzo[b]thienylmethyl,
- 2-furylmethyl,
- 2-(methylthio)ethyl,
- 2-(methylsulfinyl)ether or
- 2-(methylsulfonyl) ether;

R^3, R^{3*}, R^4, R^{4*}, R^6, R^{6*}. R^{10} and R^{10*}

mean hydrogen;

R^5 and R^{5*}

independent of each other stand for

- hydrogen,
- hydroxy or

- amino;

R^7 means

- hydrogen or
- methyl;

R^8 and R^{8*}

independent of each other mean

- hydrogen or

together with R^9 or R^{9*} and the atoms carrying these form a 1,2,3,4-tetrahydroisoquinoline or 2-azabicyclooctane skeleton;

R^9 and R^{9*}

independent of each other are defined like R^2 or R^{2*} or mean

- hydroxy,
- acetoxy,
- tert.-butoxymethyl,
- 3-guanidinopropyl,
- carbamoylmethyl, carbamoylethyl,
- carboxymethyl, carboxyethyl,
- mercaptomethyl,
- (1-mercapto-1-methyl)ethyl,
- aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl,
- N,N-dimethylamino,
- N,N'-di-(benzyloxycarbonyl)-guanidino-propyl,
- 2-benzyloxycarbonylethyl, benzyloxycarbonylmethyl,
- tert.-butylsulfonylmethyl

or

- 4-benzylcarbonylaminobutyl;

R^{11} and R^{11*}

independent of each other mean

- hydrogen,

- hydroxy or

- acetoxy,

and in the aforementioned compounds of this invention one or more amide groups (-CONH-) of the main chain can be replaced by $-CH_2NR_{14}-$ or $-CH(OH)CH_2-$;

R^{14} stands for

- hydrogen or

- methyl;

as well as their physiologically tolerated salts.

Very particularly preferred are compounds of formula I

wherein R^1 and R^{1*}

independent of each other stand for

$-a_1$) - hydrogen,

- carboxyl,

- (C_1-C_{16})-alkylsulfonyl, such as

- methylsulfonyl,

- tert.-butylsulfonyl,

- isopropylsulfonyl or

- hexadecylsulfonyl,

- (C_1-C_8)-mono- or -dihydroxyalkylsulfonyl, such as

- 2-hydroxyethylsulfonyl or

- 2-hydroxypropylsulfonyl,

- mono-, di- or trihydroxy-(C_1-C_3)-alkyl, such as

- 1,2,3-trihydroxypropyl,

- 1,2-dihyrdoxyethyl or
- hydroxymethyl,
- (C_1-C_8)-alkoxycarbonyl, such as
- methoxycarbonyl,
- ethoxycarbonyl,
- isobutoxycarbonyl or
- tert.-butoxycarbonyl,
- (C_1-C_{14})-alkanoyl, such as
- tetradecanoyl,
- amino-(C_1-C_{12})-alkanoyl, such as
- 12-aminododecanoyl,
- (C_1-C_{10})-aryloxy-(C_1-C_4)-alkylcarbonyl, such as
- 1- or 2-naphthyloxyacetyl,
- (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonyl, such as
- Benzyloxycarbonyl or
- 1- or 2-naphthylacetyl,
- 9-fluorenylmethoxycarbonyl,
- (C_1-C_4)-alkanoyloxy-(C_1-C_6)-alkyl, such as
- acetoxymethyl,
- 1,2-diacetoxyethyl,
- 1,2,3-triacetoxypropyl,
- phenyl
- benzolslfonyl possibly substituted by halogen, amino, (C_1-C_4)-alkyl or methoxy, such as
- benzolsulfonyl or
- 4-methylphenylsulfonyl,

- benzolsulfonyl, -sulfinyl or - thio possibly substituted by halogen, amino, (C_1-C_4)-alkyl or methoxy, such as

- 4-chlorobenzylsulfonyl,

- benzylsulfinyl or

- 4-chlorobenzylthio,

- het, such as

- 2- or 4-pyridyl or

- 2- or 4-(N-oxidopyridyl),

- het-sulfonyl, such as

- 4-tert.-butoxycarbonylamino-1-piperidylsulfonyl or

- 4-amino-1-piperidylsulfonyl,

- het-(C_1-C_4)-alkylsulfonyl, such as

- 2-(4-pyridyl)-ethylsulfonyl,

- het-(C_1-C_4)-alkanoyl, such as

- 2-pyridylacetyl,

- 3-pyridylacetyl,

- 4-tert.-butoxycarbonylamino-1-piperidylcarbonyl,

- 4-amino-1-piperidylcarbonyl or

- 2-quinolylcarbonyl,

- het-mercapto-(C_1-C_3)-alkylcarbonyl, such as

- 2-pyridylthioacetyl,

het in each case standing for

- pyrrolyl,

- imidazolyl,

- pyridyl,

- pyrimidyl,

- pyrrolidyl,
- quinolyl,
- isoquinolyl,
- piperidyl or
- morpholino,

it also being possible that this radical is substituted by one or two identical or different radicals from the group methyl, amino and (C_1-C_4)-alkoxycarbonylamino,

- amino-(C_3-C_6)-cycloalkylcarbonyl, such as
- 2-aminocyclopropylcarbonyl,
- 3-aminocyclobutylcarbonyl,
- 3-aminocyclopentylcarbonyl,
- 4-aminocyclohexylcarbonyl,
- (C_1-C_8)-alkanoyl, which is substituted by hydroxy and amino and possibly by phenyl or cyclohexyl, such as

2-amino-1-hydroxy-4-methyl-pentyl-

- possibly protected amino-substituted phenyl- or cyclohexyl-(C_1-C_6)-alkyl, such as
- 2-amino-3-phenyl-propyl or
- N-tert.-butoxycarbonyl-2-amino-3-phenyl-propyl,
- amino,
- (C_1-C_4)-alkoxycarbonylamino,
- benzyloxycarbonylamino,
- 1-deoxyhexoketosyl or 1-deoxypentoketosyl, such as
- 1-deoxyfructos-1-yl, 1-deoxysorbos-1-yl or
- 1-deoxyribulos-1-yl,

- hexosyl or pentosyl, such as

- mannosyl, glucosyl or galactosyl, or

- xylosyl, ribosyl or arabinosyl, it being possible for the joined sugar to be present in the pyranose or the furanose form,

R^2 and R^{2*}

independent of each other stand for

- hydrogen,

- methyl, ethyl, isopropyl, n-propyl, n-butyl, isobutyl, sec.-butyl, pentyl, hexyl,

- cyclopentylmethyl, cyclohexylmethyl,

- 4-methylcyclohexylmethyl,

- benzyl,

- 2-phenylethyl,

- 1-naphthylmethyl, 2-naphthylmethyl,

- 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl,

- 2,4,6-trimethylbenzyl,

- 4-tert.-butylbenzyl,

- 4-methoxybenzyl,

- 3,4-dihydroxybenzyl,

- 2,4-dimethoxybenzyl,

- 3,4-dimethoxybenzyl,

- 3,4-dimethylenedioxylbenzyl,

- 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl or

- 2-(4-pyridyl)ethyl;

R^3, R^{3*}, R^4, R^{4*}, R^6, R^{6*}, R^7, R^{10} AND R^{10*}

mean hydrogen;

R^5 and R^{5*}

independent of each other mean

- hydrogen or
- hydroxy;

R^8 and r^{8*} independent of each other are defined as on page 36,

R^9 and R^{9*}

independent of each other are defined like R^9 an R^{9*} on page 36;

R^{11} and R^{11*} independent of each other are defined as on page 37,

as well as their physiologically tolerated salts.

Also preferred in particular are compounds of formula I in which

Y stands for a radical of formula III;

l means 0 or 1;

m means 1;

A, A*, D and D* are defined as above;

n, n*, o, o*, p and p* independent of one another mean 1;

E, E*, F, F*, G and G* independent of one another stand for an amino acid from the series Val, Lys, Lys(Z), Phe, Chg, Ser, Asn, Gly, Ile, Tbg, Nva or Npg;

R^1 and R^{1*} independent of each other mean

- hydrogen,
- carboxyl,
- methylsulfonyl,
- tert.-butylsulfonyl,
- tert.-butoxycarbonyl,
- 2-hydroxyethylsulfonyl,
- 1,2,3-trihydroxypropyl,
- 1,2,3-triacetoxypropyl,

- benzyloxycarbonyl,
- 4-methylphenylsulfonyl,
- 4-chlorobenzylthio,
- benzylsulfinyl,
- 4-chlorobenzylsulfonyl,
- hexadecylsulfonyl,
- 4-amino-1-piperidyl-sulfonyl,
- N-tert.-butoxycarbonyl-4-amino-1-piperidyl-sulfonyl,
- 4-amino-1-piperidyl-carbonyl,
- N-tert.-butoxycarbonyl-4-amino-1-piperidyl-carbonyl,
- 2-amino-3-phenyl-propyl,
- N-tert.-butoxycarbonyl-2-amino-3-phenyl-propyl,
- 2-amino-1-hydroxy-4-methyl-pentyl,
- deoxyfructos-1-yl,
- mannofuranosyl,
- 4-aminocyclohexylcarbonyl,
- 2-quinolylcarbonyl,
- 1-naphthylacetyl,
- 1-naphthyloxyacetyl,
- 1-(4-pyridyl)-ethylsulfonyl,
- 12-aminododecanoyl,
- 4-(N-oxidopyridyl),
- 4-pyridyl,
- tetradecanoyl,
- 2-pyridylacetyl,
- 4-pyridylthio-acetyl,

- phenyl,

- amino or

- tert.-buroxycarbonylamino;

R^2 and R^{2*} independent of each other mean

- hydrogen,

- 2-(4-pyridyl)ethyl,

- isopropyl,

- isobutyl,

- n-pentyl,

- benzyl,

- 3,4-methylenedioxybenzyl,

- 2,4-dimethoxybenzyl,

- 4-tert.-butylbenzyl,

- 2-phenylethyl or

- cyclohexylmethyl;

R^3, R^{3*}, R^4. R^{4*}, R^6, R^{6*}, R^7, R^{10} and R^{10*} mean

- hydrogen;

R^5 and R^{5*} independent of each other mean

- hydrogen or

- hydroxy;

R^8 and R^{8*} mean

- hydrogen, or together with R^9 or R^{9*} and the atoms carrying these form a 1,2,3,4-tetrahydroquinoline-3,4-diyl system;

R^9 and R^{9*} independent of each other mean

- hydrogen,

- hydroxy,

- acetoxy,
- n-propyl,
- isopropyl,
- isobutyl,
- aminomethyl,
- 4-aminobutyl,
- hydroxymethyl,
- tert.-butoxymethyl,
- aminocarbonylmethyl,
- 2-benzyloxycarbonyl-ethyl,
- 4-benzylcarbonylamino-butyl,
- N,N*-di(benzyloxycarbonyl)-guanidino-propyl,
- cyclohexyl,
- cyclohexylmethyl,
- benzyl,
- 2-phenyl-ethyl,
- 4-hydroxy-benzyl,
- 4-methoxy-benzyl,
- 4-tert.-butoxy-benzyl,
- 1-naphthylmethyl,
- 2-thienylmethyl,
- 1-imidazolyl-methyl,
- 3-indolyl-methyl,
- 4-pyridylmethyl,
- 4-(N-oxidopyridyl)methyl,
- 2-methylthio-ethyl,

- 2-methylsulfonyl-ethyl,

- tert.-butylsulfonyl-methyl or

- 2-carboxyl-ethyl;

R^{11} and R^{11*} independent of each other mean

- hydrogen or

- acetoxy;

it being possible in the aforementioned compounds that one or more amide groups (-CONH-) of the main chain are replaced by $-CH_2NH-$ or $-CH(OH)CH_2-$; as well as their physiologically tolerated salts.

Also cited as being very preferred are compounds of formula I in which

l = 0;

m = 1;

n + o + p = 1;

D and D* stand for a radical of formula VI or VI*;

R^1 and R^{1*} mean

- (C_1-C_{12})-alkylsulfonyl, which can possibly be substituted by up to 3 identical or different radicals from the series

- hydroxy,

- amino or

- carboxy;

R^2 and R^{2*} independent of each other mean

- hydrogen,

- carboxyl,

- methyl, ethyl, isopropyl, n-propyl, n-butyl, isobutyl, sec.-butyl, pentyl, hexyl,

- cyclohexyl,

- cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl,
- 4-methylcyclohexylmethyl,
- 1-decahydronaphthylmethyl, 2-decahydroanaphthylmethyl,
- phenyl,
- benzyl,
- 2-phenylethyl,
- 1-naphthylmethyl, 2-naphthylmethyl,
- 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl,
- 2,4,6-trimethylenzyl,
- 4-tert.-butylbenzyl,
- 4-tert.-butoxybenzyl,
- 4-hydroxybenzyl,
- 4-methoxybenzyl,
- 2,4-dimethoxybenzyl,
- 3,4-dihydroxybenzyl,
- 3,4-dimethoxybenzyl,
- (benzodioxolane-4-yl)methyl,
- 4-chlorobenzyl,
- hydroxymethyl,
- 1-hydroxyethyl,
- 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-(4-pyridyl)ethyl,
- 2-thienylmethyl, 3-thienylmethyl,
- 2-(2-thienyl)ethyl, 2-(3-thienyl)ethyl,
- indole-2-yl-methyl, indole-3-yl-methyl,
- (1-methyl-imidazole-4-yl)methyl,
- 2-thiazolylmethyl,

- 3-pyrazolylmethyl,

- 4-pyrimidylmethyl,

- 2-benzo[b]thienylmethyl, 3-benzo[b]thienlymethyl,

- 2-furylmethyl,

- 2-(methylthio)ethyl,

- 2-(methylsulfinyl)ethyl or

- 2-(methylsulfonyl)ethyl;

R^3, R^{3*}, R^4, R^{4*}, R^6, R^{6*}, R^{11} an R^{11*} mean

- hydrogen;

R^5 and R^{5*} mean

- hydroxy;

R^9 and R^{9*}

are defined like R^9 and R^{9*} on page 44;

as well as compounds of formula I in which

l = 0;

m = 1;

n + o + p = 1;

D and D* stand for the radical of formula VII or VII*;

R^1 and R^{1*}

mean a hexosyl or pentosyl radical or a 1-deoxyhyxocetosyl or 1-deoxypentoketosyl radical which is defined as above;

R^2 and R^{2*} mean

- hydrogen,

- $(C_1\text{-}C_8)$-alkyl,

- $(C_3\text{-}C_{10})$-cycloalkyl-$(C_1\text{-}C_6)$-alkyl or

- (C_6-C_{10})-aryl-(C_1-C_4)-alkyl, each of which can be substituted with up to 3 identical or different radicals from (C_1-C_4)-alkyl or (C_1-C_4)-alkoxy;

R^3, R^{3*}, R^4, R^{4*}, R^6, R^{6*}, R^{11} and R^{11*} mean

- hydrogen;

R^5 and R^{5*} mean hydroxy;

R^9 and R^{9*} are defined like R^9 and R^{9*} on page 44.

The present invention furthermore concerns a process for the preparation of compounds of formula (I) characterized in that a fragment with terminal carboxyl group or its reactive derivative is coupled to a corresponding fragment with free amino group, for protection of other functional groups a temporarily inserted protective group(s) is split off and the compound thus obtained is, if appropriate, converted into its physiologically tolerated salt.

Fragments of a compound of formula (I) with a terminal carboxyl group have, for example, the following formulas:

D - OH (VIII)

D - E - OH (IX)

D - F - OH (X)

D - G - OH (XI)

D - E - F - OH (XII)

D - E - G - OH (XIII)

D - F - G - OH (XIV)

D - E - F - G - OH (XIVa)

This applied correspondingly for the radicals indicated by an asterisk.

Fragments of a compound of formula (I) with a final amino group have, for example, the following formulas:

H - Z - H (XV)

H - G - Z - G* - H (XVI)

H - F - Z - F* - H (XVIa)

H - E - Z - E* - H (XVIb)

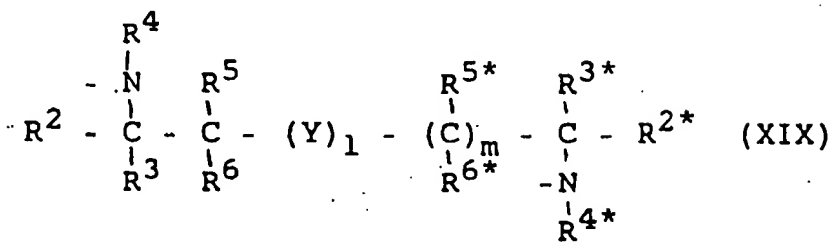
H - F - G - Z - G* - F* - H (XVII)

H - E - G - Z - G* - E* - H (XVIIa)

H - E - F - Z - F* - E* - H (XVIIb)

H - E - F - G - Z - G* - F* - E* - H (XVIII),

Z standing for a radical of formula (XIX):



(XIX)

In case of non-symmetrical target molecules it is also possible to use fragments other than those of formulas XV to XVIII which may be protected at a terminal amino group.

Methods suitable for producing an amide bond are described, for example, in Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), vol. 15/2; Bodanszky, et al., Peptide Synthesis, 2nd ed. (Wiley & Sons, New York 1976) or Gross, Meienhofer, The Peptides: Analysis, synthesis, biology (Academic Press, New York 1979). Preferably the following methods are used: active ester method with N-hydroxy-succinimide, 1-hydroxybenzo-triazole or 3-hydroxy-4-oxo-3,4-dihydro-1,2,3-benzotriazine as alcohol component,

coupling with a carbodiimide such as dicyclo-hexylcarbodiimide (DCC) or with n-propanephosphonic anhydride (PPA) and the mixed-anhydride method with pivaloylchloride or chloroformic ethyl ester or -isobutyl ester, or coupling with phosphonium reagents such as benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP) or uronium reagents such as 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoro-borate (TBTU).

Fragments of formula (VIII) or (VIII*) if they fall under

a) formula (V) or (V*) are synthesized according to the general methods for the preparation of amino acids;

b) formula (VI) or (VI*) are synthesized, for example, proceeding from the corresponding amino acids, their chirality center being preserved. Diazotizing at -20°C to 50°C in dilute mineral acids leads to α-bromocarboxylic acid or via the lactic acids to α-trifluoromethanesulfonyloxy carboxylic acid which can be reacted with a neuclophile bearing an R^1 and R^{11} or R^{1*} and R^{11*}, or are prepared, for example, proceeding from malonic esters, the alkylation of which produces mono- or di-substituted malonic esters which, after saponification by decarboxylation, are converted into the desired derivatives.

c) Formula (VII) or (VII*) are synthesized proceeding from the corresponding α-amino acids, their chirality center being preserved. Diazotizing at -20°C to 50°C in dilute mineral acids leads to lactic acids which can be reacted with an electrophile bearing R^1 or R^{1*}.

Fragments of formulas (IX), (X), (XI), (XII) and (XIII), (XIV) and (XIVa) are synthesized according to the generally known methods for the preparation of amino acids and peptides.

Fragments of formula (XV) are synthesized proceeding from optically active α-amino acids or sugars or their derivatives. For example, for the preparation of fragments with m = 1, l = 0, $R^5 = R^{5*}$ = OH and $R^6 = R^{6*}$ = H the amino acids are converted in known manner into N-protected amino acid aldehydes (B. Castro, et al., Synthesis 1983, 676) and reductively reacted with suitable metals, metallic salts, or also electrochemically to N-protected diaminodiols. For this, for example, the N-protected aldehydes are dissolved in tetrahydro-furan and at -30°C to 60°C, preferably -10°C to 30°C are converted into the N-protected diaminodiols by the addition of a solution of samarium(II) iodide in tetrahydrofuran.

With synthesis from sugar (derivatives) the chirality centers of the initial material are preserved or inverted. OH groups that are to be preserved are protected in suitable manner; the others are activated by reaction with, for example, a sulfonic acid chloride or according to Mitsunobu (Synthesis (1981), 1-28) and can be exchanged by nucleophiles. The desired products are obtained here in stereochemically uniform form.

Proceeding, for example, from D-mannitol the hydroxy groups of the polyol in positions 3 and 4 are protected by treatment with acetone/sulfuric acid and subsequently with aqueous acetic acid as acetonide. By reaction of the two terminal OH groups with p-toluenesulfonyl chloride/pyridine and treatment with potassium carbonate in methanol one obtains the 1,2R-5R,6-diepoxide-3,4-O-isopropylidene-3R,4R-diol (Y. Le Merrer, et al., Tetrahedron Lett. 26 z(1985) 319-322). Treatment of the diepoxide with cuprates in, for

example, tetrahydrofuran leads to opening of the epoxides and introduction of substituents in positions 1 and 6. After activation of the hydroxy groups in positions 2 and 5 by reaction with, for example, a sulfonyl chloride both are exchanged by reaction with an azide. Reduction of the two azide groups by, for example, catalytic hydrogenation and splitting off the acetonide protective group with HCl/methanol produces the compounds of radical (XV).

Fragments of formula (XV) with m = 1, l = 1 and Y = radical of formula III are obtained in such a manner that N-protected amino acid aldehydes (see above) are reacted under reductive conditions (e.g. $NaBH_3CN$) with a suitable amine.

Here the aldehydes are dissolved, e.g. in methanol, and reacted with, for example, sodium cyanoborohydride as reductant. Subsequent splitting off of the protective groups yields the desired building block.

Fragments of formula XV with m = 0, l = 0, R^5 = OH, R^6 = H are obtained in such a manner that suitable nitro compounds are deprotonated with bases such as tetramethylguanidine and added to N-protected amino acid aldehydes (see above). Reduction of the nitro group with, for example, Raney nickel and splitting off the protective groups yields the compounds of formula (XV) as diastereomers which are separated as described above.

The fragments of formulas XVI, XVIa, XVIb, XVII, XVIIa, XVIIb AND XVIII are synthesized according to generally known methods for the preparation of amino acids and peptides.

In the compounds of formula I one or more amide groups can be replaced by $-CH_2NR^{14}-$, $-CH_2S-$, $-CH_2O-$, OCH_2-, $-CH_2CH_2-$, -CH=CH- (cis and trans), $-COCH_2-$, $-CH(OH)CH_2-$, $-CH_2SO-$, $-CH_2SO_2-$, -COO-, $-P(O)(OR^{15})CH_2-$, $-P(O)(OR^{15})_2NH-$ or -NH-CO-.

Peptide analogs of this type can be prepared according to known processes, which can be found, for example, in the following literature sources:

A. F. Spatola in "Chemistry and Biochemistry of Amino Acids, Peptides and proteins" 1983 (B. Weinstein, et al. eds.) Marcel Dekker, New York, p. 267 (review article).

J. S. Morley, Trends Pharm. Sci. (1980) pp. 463-468 (review article).

D. Hudson, et al., Int. J. Pept. Prot. Res. (1979), 14, 177-185, ($-CH_2NH-$, $-CH_2CH_2-$);

A. F. Spatola, et al., Life Sci. (1986) 38, 1243-1249 ($-CH_2-S-$);

M. M. Hann, J. Chem. Soc. Perkin Trans.I (1982) 307-314 (-CH=CH-, cis and trans);

J. K. Whitesell, et al., Chirality 1 (1989) 89-91 (-CH=CH-, cis and trans);

R. G. Almquist, et al., J. Med. Chem. (1980) 23, 1392-1398 ($-COCH_2-$);

C. Jennings-White, et al., Tetrahedron Lett. (1982) 23, 2533 ($-COCH_2-$);

M. Szelke, et al., EP-A-45665 (1982), CA: 97: 39405 ($-CH(OH)CH_2-$);

M. W. Holladay, et al., Tetrahedron Lett. (1983) 24, 4401-4404 ($-CH(OH)CH_2-$);

V. J. Hruby, Life Sci. (1982) 31, 189-199 ($-CH_2-S-$);

N. E. Jacobsen, P. A. Barlett, J. Am. Chem. Soc. (1981) 103, 654-657 (-P(O)(OR)NH-).

The preliminary and subsequent operations such as introduction and splitting off of protective groups are known from literature and are described in, for example, T. W. Greene "Protective Groups in Organic Synthesis" (John Wiley & Sons, New York, 1981). Salts of compounds of formula I with salt-forming groups are produced in known manner in that, for example, a compound of formula I with a basic group is reacted with a stoichiometric amount of a

suitable acid, or compounds of formula I with an acid group are reacted with a stoichiometric amount of a suitable base. Stereoisomer mixtures, especially diastereomer mixtures, possibly produced in the synthesis of compounds of formula I, can be separated in known manner by fractionated crystallization or through chromatography.

The compounds of formula I according to the invention exhibit enzyme-inhibiting properties. In particular, they inhibit the action of retroviral aspartyl proteases such as those of the HIV proteases. Their enzyme-inhibiting effect, which lies in the milli- to subnano-molar range, can be determined as follows.

Test principle:

Among others, the heptapeptide H-Ser-Phe-Asn-Phe-Pro-Gin-Ile-OH (P. L. Darke, et al., Biophys. Res. Commun. 156 (1988) 297-303) has been used as substrate of the HIV protease. The HIV protease splits the substrate between the second Phe and Pro.

Surprisingly, it has now been found that substitution of proline by 5-oxaproline in this sequence leads to a substrate which can be split by the HIV protease considerably faster and thus permits a faster analysis with lesser enzyme requirement.

General instructions for the testing of inhibitors of HIV proteases

a) Preparation of the substrate solution:

2 mg H-Ser-Phe-Asn-Phe-Opr-Gln-Ile-OH (H-Opr-OH = 5-oxaproline) are dissolved in 1 ml MGTE-15 buffer (possible use of ultrasound) and then filtered via a sterile filter (0.45 µm).

b) Preparation of the inhibitor solution:

Of the inhibitor, 2.5 times the desired molarity per ml solution are weighed and dissolved with DMSO (10% of the final volume). The solution is diluted with MGTE-15 buffer up to the final volume and filtered via sterile filter (0.45 µm).

c) Preparation of the protease solution:

5 µl of the HIV protease solution are diluted as needed with MGTE25 buffer.

d) Test performance:

10 µl of the substrate solution are pipetted into each test tube (16 x 100) with screw-cap. For the blind test 10 µl MGTE15 buffer containing 10% DMSO are pipetted. 10 µl each of the inhibitor solutions are added to the remaining test tubes. The solutions are incubated for 5-10 minutes at 37°C and 5 µl or the protease solution are then added to each sample. After 2 hours of reaction at 37°C 10 or 20 µl (depending on the sensitivity of the HPLC equipment) are pipetted off from each sample, poured into microvials and diluted with 120 µl of the HPLC mobile solvent.

e) Conditions for the HPLC analysis:

Mobile solvent system: 80% 0.1 M phosphoric acid pH 2.5
20% (w/w) acetonitrile
column: Merck LICHROSORB RP18 (5 µm) 250x4
flow: 1 ml/min
temperature of the column: 42°C
detector parameters: 215 nm, 0.08 AUF, 18.2°C
analysis time: 11 minutes
retention time of the substrate: 8.1 minutes
retention time of the N-terminal tetrapeptide: 3.9 minutes.

f) Solvents needed:

1) MGTE15 buffer:

20 mmol morpholinoethane sulfonic acid (MES)

15% (w/v) glycerol

0.1% (v/v) Triton X 100

5 mmol EDTA

0.5 M NaCl

1 mmol phenylmethylsulfonylfluoride (PMSF)

2) MGTE25 buffer:

composition similar to MGTE15 buffer with following deviation:

25% (w/v) glycerol,

additionally 1 mmol dithiothreitol (DTT)

MES, EDTA, NaCl, DTT and PMSF are weighed into an Erlenmeyer flask, dissolved in a little water and the pH is adjusted to 6. The corresponding amount of glycerol is weighed into a measuring flask and Triton® X 100 is pipetted thereto. The aqueous solution is transferred to the measuring flask and the flask is filled with water.

3) HPLC solvent:

A 0.1 M solution is prepared from ortho-phosphoric acid (FLUKA puriss. p.a.). With triethylamine (FLUKA puriss. p.a.) this solution is adjusted precisely to pH 2.5. The weight of the solution is determined and the appropriate weighed amount of acetonitrile (escape!) is added. Mix well and degas about 5 minutes with helium 5.0.

g) Evaluation:

Under the conditions selected here the heptapeptides separate from the N-terminal tetrapeptide resulting from enzymatic splitting. The % content of the tetrapeptide peak with reference to sum tetrapeptide + heptapeptide corresponds to the splitting rate. The subsequent IC_{50} values indicate at which inhibitor concentration the splitting rate is halved.

Example no.	IC_{50}	Example no.	IC_{50}
1	10 nm	18	1.2 nm
5	3.6 nm	19	0.7 nm
6	8.8 nm	21	220 nm
7	18 nm	25	18 µm
8	30 µm	28	3 µm
10	17 nm	30	30 nm
11	0.8 nm	33	20 µm
13	1.3 nm	39	1.3 nm
14	1.0 nm	40	13 nm
15	400 nm	43	1.0 nm
16	0.85 nm	45	1.5 µm
17	0.85 nm	48	80 µm

Example no.	IC_{50}	Example No.	IC_{50}
49	1.2 nm	104	24 nm
50	45 nm	105	19 nm
51	0.8 nm	106	85 nm
52	3.2 nm	107	8.5 nm
53	4.0 nm	108	280 nm
54	260 nm	109	5.0 nm
55	1.3 nm	110	1.0 nm
58	49 nm	113	40 nm
59	47 nm	115	2.2 µm
61	400 nm	116	1.7 nm
63	6.5 nm	117	19 nm
65	1.8 nm	118	1.2 nm
72	30 nm	119	10 µm
74	1.7 nm	120	2,0 nm
75	19 nm	121	22 nm
76	0.29 nm	123	32 nm
77	9.2 nm	124	11 nm
78	1.8 nm	125	0.75 nm
80	28 nm	127	46 nm
82	9 nm	131	40 µm
83	10 nm	132	20 µm
84	110 nm	142	140 nm
85	1.9 nm	143	2.2 nm
86	2.2 nm	145	95 nm
87	1.6 nm	146	100 nm
88	1 µm	148	36 nm
89	1.8 nm	149	360 nm
90	2.2 nm	150	95 nm
91	1.3 nm	151	4 nm
93	22 nm	152	1 nm
94	6.5 nm	154	1 nm
95	380 nm	155	10 nm
97	36 nm	156	30 nm
98	1 µm		
99	15 nm		
100	400 nm		
101	1.4 nm		
102	38 nm		

The target peptide was built up in steps with a peptide synthesizer Model 430 A by the firm of Applied Biosystems using the Fmoc method on a p-benzyloxybenzylalcohol resin esterified with Fmoc-Ile-OH from the firm of Novabiochem (charge about 0.5 mmol/g resin). 1 g of the resin was used and the synthesis was carried out with the aid of synthesis program modified for the Fmoc method.

The following amino acid derivatives are used: Fmoc-Gln-OH, Fmoc-Opr-OH, Fmoc-Phe-OObt, Fmoc-Asn-OH and Fmoc-Ser(tBu)-OObt. For the synthesis of Fmoc-Opr-OH, H-Opr-OtBu was synthesized according to the method of Vasella, et al. (J. C. S. Chem. Comm. 1981, 97-98) and reacted with Fmoc-OSu in dioxane/water (1:1) in the presence of $NaHCO_3$. The subsequent splitting of the tert.-butylester with trifluoroacetic acid produces Fmoc-Opr-OH.

In each case 1 mmol of the amino acid derivatives with free carboxyl group together with 0.95 mmol HOObt was weighed into the cartridges of the synthesizer. The preactivation of these amino acids was accomplished directly in the cartridges by dissolving in 4 ml DMF and addition of 2 ml of a 0.55 molar solution of diisopropylcarbodiimide in DMF. The HOObt esters of the other amino acids were dissolved in 6 ml NMP and then like the in situ preactivated amino acids were coupled to the resin previously deblocked with 20% piperidine in DMF. At the conclusion of the synthesis the peptide was then split off from the resin with simultaneous removal of the lateral-chain protective groups using thioanisole and ethanedithiol as cation trap. The residue obtained after withdrawing the trifluoroacetic acid was digested several times with acetic ester and centrifuged.

The remaining residue was chromatographed on an alkylated dextran gel with 10% acetic acid. The fraction containing the pure peptide was combined and freeze-dried.

Mass spectrum (FAB): 854 ($M + H^+$)

Amino acid analysis Asp: 0.98; Ser: 0.80; Glu: 1.00; Ile: 1.05; Phe: 2.10; NH_3: 1.76.

The invention also concerns the use of the compounds of formula I as drugs and pharmaceutical preparations that contain these compounds. Use in primates, especially humans, is preferred.

Pharmaceutical preparations contain an effective amount of the effective substance according to formula I together with an inorganic or organic pharmaceutically usable carrier substance. Application can be intranasal, intravenous, subcutaneous or peroral. Dosing of the effective substance depends on the homoiotherm species, the body weight, age and on the type of application.

The pharmaceutical preparations of the present invention are produced in known dissolving, mixing, granulating or coating processes.

For an oral application form the active compounds are mixed with the usual additives such as carrier substances, stabilizers or inert diluents, and brought into suitable administration forms such as tablets, coated pills, insert capsules, aqueous, alcoholic or oily suspensions or aqueous, alcoholic or oily solutions. As inert carriers it is possible to use, for example, gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose, magnesium stearylfumarate or starch, especially corn starch. The preparation can be accomplished as dry or moist granulate. Oleaginous carriers can be, for example, animal or vegetable oils such as sunflower oil or cod-liver oil.

For subcutaneous or intravenous application the active compounds or their physiologically tolerated salts with, if desired, the usual substances such as solution mediators, emulsifiers or other adjuvants are brought into solution, suspensions or emulsions. Possible solvents are, for example, water, physiological saline solutions or alcohols such as ethanol, propanediol or glycerol, also sugar solutions such as glucose or mannitol solutions or also a mixture of the various solvents cited.

Likewise possible is the use of injectable delayed-release preparations. As drug forms it is possible to use, for example, oleaginous crystal suspensions, microcapsules, rods or implants. The latter two can be of tissue-compatible polymers, especially biodegradable polymers such as those on the basis of polylactic acid-polyglycolic acid copolymers or human albumin.

List of abbreviations used:

Chg: cyclohexylglycyl

Boc: tert.-butyloxycarbonyl

D: doublet

TLC: thin-layer chromatography

DCC: dicyclohexylcarbodiimide

DCM: dichloromethane

DMF: dimethylformamide

DMAP: 4-dimethylaminopyridine

DMSO: dimethyl sulfoxide

EDAC: 1-(3-dimethylamino-propyl)-3-ethyl-carbodiimide hydrochloride

EA: ethyl acetate

FAB: fast atom bombardment

HOBt: hydroxybenzotriazole

i. vac.: in a vacuum

m: multiplet

M: molecular peak

NEM: N-ethylmorpholine

Npg: neopentylglycyl

MS: mass spectroscopy

PPA: n-propylphosphonic anhydride

RT: room temperature

s: singlet

m.p.: melting point

t: triplet

Tbg: tert.-butylglycyl

TBTU: 2-(1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate

THF: tetrahydrofuran

Thia: 2-thienylalanyl

Z: benzyloxycarbonyl

The other abbreviations used for amino acids correspond to the three-letter code customary in peptide chemistry (as described, for example, in Eur. J. Biochem. 138 (1984), 9-37. Unless expressly stated otherwise, an amino acid of the L configuration is always involved.

The following examples serve to explain the present invention without restricting it.

Example 1

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

100 mg N,N'-bis-(L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride together with 111 mg N-tert.-butoxycarbonyl-L-phenylalanine, 0.57 ml NEM and 60 mg HOBt were dissolved in 1.5 ml DMF. After addition of 85 mg EDAC at 0°C the solution was stirred further for 1 h at 0°C and then overnight at RT. The solvent was spun off i. vac., the residue was taken up in EA and extracted with saturated $KHCO_3$-10% $KHSO_4$ solution and water. The organic phase was dried with anhydrous Na_2SO_4 and concentrated. The residue was recrystallized from ethanol-water.

The yield was 92 mg.

MS (FAB): 993 $(M + H)^+$, 975, 893, 793

NMR (270 MHz, DMSO <D_6>): 0.72 (d, 6 Hz, 6H); 0.75 (d, 6Hz, 6H); 1.29 (s, 18H); 1.86 (m, 2H); 2.60-2.96 (m, 8H); 3.30 (m, 2H); 4.17 (m, 2H); 4.45 (m, 2H); 4.68 (m, 2H); 7.03 (d, 9Hz, 2H); 7.05-7.30 (m, 22H); 7.53 (d, 9Hz, 2H).

Example 2

N,N'-bis-(L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol-dihydrochloride

220 mg N,N'-bis-(tert.-butoxycarbonyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-3,4-O-isopropylidene-hexane-3R,4R-diol in 10 ml of an approximately 3N solution of HCl in dioxane/methanol 1/1 were stirred for 1 h at RT. The volatile components of the solution were removed i. vac. and drying was accomplished in a high vacuum. The substance was used in the next step without further refining.

Yield: 184 mg

MS (FAB): 499 $(M + H)^+$, 481, 463

Example 2a

N,N'-bis-(tert.-butoxycarbonyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-3,4-O-isopropylidene-hexane-3R,4R-diol

136 mg 2S,5S-diamino-1,6-diphenyl-3,4-O-isopropylidene-hexane-3R,4R-diol with 0.54 ml NEM and 260 mg N-tert.-butoxycarbonyl-L-valine were dissolved in 2 ml dry EA. At -10°C 0.97 ml of a 50% PPA solution in EA were added. The solution was stirred for 1 h at 0°C and then overnight at RT. The solution was diluted with EA and extracted with saturated $NaHCO_3$, 10% $KHSO_4$ solution and water. The organic phase was dried over anhydrous $MgSO_4$, concentrated and the residue was refined by chromatography on silica gel (dichloromethane/methanol 97/3).

The yield was: 230 mg

MS (FAB): 739 $(M + H)^+$, 681, 639, 569, 539

Example 2b

2S,5S-diamino-1,6-diphenyl-3,4-O-isopropylidene-hexane-3R,4R-diol

2.3 g 2S,5S-diazido-1,6-diphenyl-1,6-O-isopropylidene-hexane-3R,4R-diol were dissolved in 50 ml methanol and hydrogenated with about 0.2 g palladium on carbon (10%) for 2 h under normal pressure. The catalyst was filtered off and after concentration of the solution the residue was chromatographed on silica gel (dichloromethane/methanol 99/1).

Yield: 1.33 g

MS (FAB): 341 $(M + H)^+$

NMR (270 MHz; DMSO <D_6>): 1.29 (m, 4H), 1.37 (s, 6H); 2.71 (dd, 12Hz, 5 Hz, 2H); 2.87 (m, 2H); 3.32 (m, 2H); 3.95 (s, 2H); 7.12-7.33 (m, 10H)

Example 2c

2S,5S-diazido-1,6-diphenyl-3,4-O-isopropylidene-hexane-3R,4R-diol

8.5 g 2R,5R-di-(4-nitrophenylslufonyloxy)-1,6-diphenyl-3,4-O-isopropylidene-hexane-3S,4S-diol were dissolved in 300 ml DMF and heated with about 9.2 g NaN_3 and 6.3 g 18-Krone-6 for 4 h at 50°C. Most of the solvent was spun off i. vac., the residue was taken up in ether and extracted with aqueous $NaHCO3_3$ solution. After washing with water the solution was dried and concentrated. The residue was chromatographed on silica gel (toluene/ n-heptane 2/5 to 2/3).

Yield: 2.37 g

NMR (270 MHz, DMSO <D_6>): 1.48 (s, 6H); 2.92-3.12 (m, 4H); 3.74 (dd, 10 Hz, 5 Hz, 2H); 4.15 (s, 2H); 7.21-7.39 (m, 10H)

Example 2d

2R,5R-di-(4-nitrophenylsulfonyloxy)-1,6-diphenyl-3,4-O-isopropylidene-hexane-3S,4S-diol

5.6 g 2R,5R-dihydroxy-1,6-diphenyl-3,4-O-isopropylidene-hexane-3R,4R-diol together with 7.9 g DMAP were dissolved in 300 ml chloroform. 14.5 g p-nitrobenzenesulfonyl chloride were added at RT and the solution was stirred for 3 h at 50°C. Methylene chloride was added and the solution was extracted with bicarbonate, $KHSO_4$ and NaCl solution. After drying of the organic phase it was concentrated.

Yield: 11.8 g

MS (FAB): 713 $(M + H)^+$, 697, 510

NMR (270 MHz, DMSO <D_6>): 1.42 (s, 6H); 2.87 (dd, 15Hz, 9Hz, 2H); 3.11 (dd, 15Hz, 3Hz, 2H); 4.41 (s, 2H), 5.07 (dm, 9Hz, 2H), 6.95-7.11 (m, 10H); 7.73 (d, 9Hz, 4H); 8.18 (d, 9Hz, 4H)

Example 2e

2R,5R-dihydroxy-1,6-diphenyl-3,4-O-isopropylidene-3R,4R-diol

Under argon, 1.12 g 1,2R-5R,6-diepoxy-3,4-O-isopropylidene-3R-4R-diol (Y. Le Merrer, A. Dureault, C. Gravier, D. Languin and J, C. Depezay, Tetrahedron Lett. 26 (1985) 319-322) were added at -78°C to a solution of 36 mmol $(C_6\text{-}H_5)_2CuLi$ in 60 ml dry ether. The cold bath was removed and the solution was permitted to warm to RT with stirring. 250 ml EA were added to the solution and it was extracted three times with a mixture of 25% ammonia and ammonium chloride. The EA phase was washed with NaCl solution, dried and concentrated. The residue was refined over silica gel (dichloro-methane/EA 97/3 to 90/10).

Yield: 1.86 g

MS (FAB): 343 $(M + H)^+$, 327, 285, 267

NMR (270 MHz, DMSO <D_6>): 1.39 (s, 6H); 2.58 (dd, 13Hz, 9Hz, 2H), 3.43 (dd, 13Hz, 3Hz, 2H); 3.68 (m, 2H); 3.83 (m, 2H), 5.05 (d, 6Hz, 2H); 7.14-7.32 (m, 10H)

Synthesis analogous to example 2 from example 11

MS (FAB, LiI): 761 $(M + Li)^+$, 755 $(M + H)^+$, 737

Examples 3-5

3) N,N'-bis-(tert.-butoxycarbonyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

4) N,N-bis-(tert.-butoxycarbonyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

5) N,N-bis-(tert.-butoxycarbonyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4S-diol

17 g tert.-butoxycarbonyl-L-phenylalaninal were dissolved in 500 ml THF and cooled under argon to 0°C. Over about 20 min 1 l of 0.1 molar SmI_2 solution in THF were added and the solution was stirred for 30 min at RT. The solution was acidified to pH 1-2 with 0.1 N aqueous HCl. The solution was diluted with EA, the organic phase was separated and extracted with 0.1 N HCl, twice with $Na_2S_2O_3$ solution and twice with water. After drying over $MgSO_4$ the solution was concentrated and chromatographed over silica gel (EA/petroleum ether 1/2).

The fraction containing the 3R,4R isomer was recrystallized from ethanol/water.

Through crystallization from dichloromethane/isopropyl ether/heptane it was possible to derive the 3S,4S isomer from the fraction containing the 3S,4S and the 3R,4S isomer. To obtain the 3R,4S isomer the mother liquor was chromatographed on RP18 silica gel (acetonitrile/water 4/6).

Yields: 1.61 g 3R,4R isomer

1.00 g 3S,4S isomer

0.71 g 3R,4S isomer

Rf values: silica gel, EA/hexane 1/2

0.18 3R,4R isomer

0.41 3S,4S isomer

0.39 3R,4S isomer

MS (FAB): 501 $(M + H)^+$, 401, 345, 327, 301 3R,4R isomer 501 $(M + H)^+$, 401, 345, 327, 301, 3S,4S isomer 501 $(M + H)^+$, 401, 345, 327 3R,4S isomer

^{1}H-NMR (270 Mhz, DMSO <D_6>):			
	3R,4R isomer	3S,4S isomer	3R,4S isomer
N-H	6.16; (d; 2H)	6.60 (d, 2H)	6.31 (d, 1H) 6.28 (d, 1H)
O-H	4.43 (m, 2H)	4.57 (d, 7Hz,2H)	4.62 (s, 4Hz, 1H) 4.94 (d, 6Hz, 1H)
H^3, H^4	4.12 (m, 2H)	3.71 (m, 2H)	3.91-4.12 (m, 2H)
H^2, H^5	3.24 (m, 2H)	3.42 (m, 2H)	3.27-3.46 (m, 2H)
CH_2	2.54-2.80 (m,2H)	3.04 (dd, 14Hz, 4Hz, 1H 2.63 (dd, 14Hz, 9Hz, 1H	2.62-2.83 (m, 2H)
$C(CH_3)_3$	1.30 (s, 18H)	1.30 (s, 18H)	1.32 (s, 9H) 1.24 (s, 9H)
Ar-H	7.08-7.27 (m,10H)	7.11-7.29 (m, 10H)	7.08-7,32 (m, 10H)

The correlation of the absolute stereochemistry is found for the 3R,4S isomer from twice the signal set; the differentiation between the 3R,4R and the 3S,4S isomers, by comparison with synthetic reference material proceeding from D-mannitol (see example 3.1). Evaluation of coupling constants after splitting of the tert.-butoxycarbonyl groups and conversion of the isomers with phosgene into double 2-oxazolidinone thus yielded consistent results.

Example 3.1

Correlation of the absolute stereochemistry of the isomers from examples 3-5.
N,N'-bis-(tert.-butoxycarbonyl)-2S-5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

140 mg 2S,5S-diamino-1,6-diphenyl-3,4-O-isopropylidene-hexane-3R<4R-diol were dissolved in a mixture of 5 ml 1N HCl in methanol and 5 ml 5N HCl in dioxane and stirred for 4 h at RT. The volatile components were removed i. vac. The residue was dried in a high vacuum and the 2S,5S-diamino-1,6-

diphenyl-hexane-3R,4R-diol-dihydrochloride (MS (FAB): 301 $(M + H)^+$ of the free base) obtained was used directly in the next reaction.

45 mg 2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol-dihydrochloride were dissolved in 5 ml dry dichloromethane and together with 40 µl triethylamine and 75 mg pyrocarboxylic-di-tert.-butyl ester stirred for 3 h at RT. The solution was diluted with dichloromethane and extracted with $KHSO_4$, $NaHCO_3$ and NaCl solutions. After drying over anhydrous Na_2SO_4 the solution was concentrated and purified over silica gel (acetonitrile/DCM 1/8).

Yield: 23 mg

MS (FAB) 501 $(M + H)^+$, 401, 345, 327, 301

The compound was identical to the most polar isomer from examples 3-5.

Example 6

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

38 mg N,N'-bis-(tert.-butoxycarbonyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol were treated for 30 min with 5N HCl in dioxane. The volatile components were removed i. vac., and the residue was dried. The N,N'-bis-(L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol-dihydrochloride thus obtained was dissolved with 40 mg tert.-butoxycarbonyl-phenylalanine, 22 mg HOBt and 51 mg TBTU in 1 ml dry DMF. 60 µl ethyldiisopropylamine were added and the solution was stirred for 15 min at RT. The DMF was spun off, the residue was taken up in EA and extracted with $KHSO_4$, $NaHCO_3$ solutions and water. After drying over $MgSO_4$ the solution was concentrated, the substance crystallizing out. The precipitate was filtered off, washed with ether, and a yield of 30 mg was obtained.

MS (FAB): 1015 $(M + Na)^+$, 993 $(M + H)^+$, 893, 793

NMR (270 MHz, DMSO <D_6>): 0.79 (m, 12H); 1.28 (s, 18H); 1.85 (m, 2H); 2.68-2.82 (m, 4H); 2.85-3.03 (m, 4H); 3.37 (m, 2H); 4.00-4.13 (m, 4H); 4.21 (m, 2H); 4.66 (d, 7Hz, 2H); 7.03 (d, 7Hz, 2H); 7.05-7.34 (m, 20H); 7.62 (d, 7Hz, 2H); 7.68 (d, 8Hz, 2H)

Example 7

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4S-diol

Synthesis analogous to example 6 from N,N'-bis-(tert.-butoxycarbonyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4S-diol

MS (FAB): 1015 $(M + Na)^+$, 993 $(M + H)^+$, 893, 793

NMR (270 MHz, DMSO <D_6>): 0.68-0.85 (m, 12H); 1.28 (s, 9H); 1.30 (s, 9H); 1.75-2.03 (m, 2H); approx. 2.5-3.30 (m, 8H); approx. 3.3-3.51 (m, 2H); 4.05-4.30 (m, 5H); 4.43 (m, 1H); 4.74 (d, 4Hz, 1H); 5.32 (d, 7Hz, 1H); 6.93-7.35 (m, 22H); 7.61 (d, 8Hz, 1H); 7.67 (d, 7Hz, 1H); 7.85 (d, 8Hz, 1H); 7.92 (d, 7Hz, 1H)

Example 8

N,N'-bis-(tert.-butoxycarbonyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

164 mg N,N'-bis-(tert.-butoxycarbonyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol were treated for 1.5 h at RT with 10 ml 5N HCl in dioxane. The volatile components were removed i. vac., the residue was dried. The 2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride thus obtained was dissolved in 15 ml dry DMF together with 178 mg tert.-butoxycarbonyl-L-valine

and 0.56 ml NEM. At -5°C 0.53 ml of a 50% solution of PPA in EA were added, the solution was stirred for 1 h at 0°C and overnight at RT. The solvent was spun off, the residue was taken up in EA and extracted with $NaHCO_3$, $KHSO_4$ solutions and water. After drying over Na_2SO_4 the solution was concentrated in a vacuum. The product crystallized out with treatment of the residue with diethyl ether. It was recrystallized from ethanol/water.

Yield: 59 mg

MS (FAB): 699 $(M + H)^+$, 599, 499

Example 9

N,N'-bis-(tert.-butoxycarbonyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4S-diol

Synthesis analogous to example 8 from N,N'-bis-(tert.-butoxycarbonyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4S-diol

MS (FAB): 699 $(M + H)^+$, 599, 499

Example 10

N,N'-bis-(L-lysyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol tetrahydrochloride

Synthesis analogous to example 2 from example 11

MS (FAB, LiI): 761 $(M + Li)^+$, 755 $(M + H)^+$, 737

Example 11

N,N'-bis-(Nα-<tert.-butoxycarbonyl>-L-lysyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

36 mg N,N-bis(<Nω-benzyloxycarbonyl-Nα-tert.-butoxycarbonyl>L-lysyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R diol (synthesis analogous to example 1 from Nω-benzyloxycarbonyl-Nα-tert.-butoxycarbonyl-L-lysine and N,N'-bis-(L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride) were hydrogenated in methanol with palladium on activated charcoal as catalyst. The pH value was kept at about 3-4 with a solution of HCl in methanol. After filtering off the catalyst and concentrating, 26 mg of product were obtained.

MS (FAB, LiI): 961 $(M + Li)^+$

NMR (270 MHz, DMSO <D_6>): 0.75 (d, 5Hz, 6H); 0.78 (d, 5Hz, 6H); c. 1.13-1.60 (m, c. 12H); 1.38 (s, 18H); 1.88 (m, 2H); c.l 2.50-2.68 (m, 2H); 2.72-2.94 (m, 6H); 3.72 (m, 2H); 4.22 (m, 2H); 4.37 (m, 2H); 4.41-4.55 (m, 4H); 4.72 (m, 2H); 6.76 (m, 2H); 7.05-7.23 (m, 16H); 7.66 (d, 8Hz 2H); 8.15 (d, 9Hz, 2H)

Example 12

N,N'-bis-(Nα-<tert.-butoxycarbonyl-L-phenylalanyl>-L-lysyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

Synthesis analogous to example 11.

MS (FAB): 1051 $(M + H)^+$, 951

Example 13

N,N'-bis-<(2S-(1,1-dimethylethyl-sulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

57 mg N,N'-bis-(L-valyl)-2S<5S-diamino-1,6-diphenyl-hexane-3R<4R-diol dihydrochloride, 95 mg (2S-(1,1-dimethylethylsulfonylmethyl)-3-(1-naphthyl)-

propionic acid (J. Med. Chem. 31, 1839 (1988), 41 mg HOBt and 96 mg TBTU were dissolved in 1 ml dry DMF. 0.11 ml N-ethyldiisopropylamine were added at RT and the solution was stirred for 1 h. The solvent was spun off, the residue was taken up with 30 ml EA and extracted with bisulfate and bicarbonate solutions and water. After drying over Na_2SO_4 the solution was concentrated and the substance was purified by chromatography on silica gel (DCM/methanol 97/3).

Yield: 31 mg.

MS (FAB): 1153 $(M + Na)^+$, 1131 $(M + H)^+$, 716

NMR (270 MHz, DMSO <D_6>): 0.69 (d, 7Hz, 6H); 0.76 (d, 7Hz, 6H); 1.10 (s, 18H); 1.86 (m, 2H); 2.63-2.87 (m, 6H); 3.08 (m, 2H); c. 3.25-3.44 (m, c. 2H); 3.52-3.63 (m, 2H); 4.08 (m, 2H); 7.32 (d, 8 Hz, 2H); 7.38-7.48 (m, 4H); 7.47-7.62 (m, 4H); 7.81 (m, 2H); 7.92 (m, 2H); 8.12-8.25 (m, 4H)

Example 14

N,N'-bis-(L-seryl-L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

Synthesis analogous to example 16

MS (FAB, LiI): 973 $(M + Li)^+$, 967 $(M + H)^+$

Example 15

N,N'-bis-(tert.-butoxycarbonyl-L-(O-tert.-butyl-seryl)-L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

52 mg N,N'-bis-(L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride together with 18 mg HOBt, 15.3 µl NEM and 35 mg O-tert.-butyl-N-tert.-butoxycarbonyl-L-serine were dissolved in 1 ml dry

DMF and 25.3 mg EDAC were added at 0°C. The solution was stirred for 1 h at 0°C and overnight at RT. The solvent was spun off, the residue was taken up in EA and extracted with bisulfate solution, bicarbonate solution and water. The organic phase was dried over anhydrous sodium sulfate and concentrated. The residue was purified by chromatography on silica gel.

Yield: 28 mg.

MS (FAB): 1301 $(M + Na)^+$, 1279 $(M + H)^+$, 1261, 1179, 1079.

NMR (270 MHz, DMSO <D_6>): 0.78 (d, 7Hz, 6H); 0.81 (d, 7Hz, 6H); 1.06 (s, 18H); 1.38 (s, 18H); 1.82 (m, 2H); 2.61-2.98 (m, 8H); 3.15-3.45 (m, c. 6H); 3.92 (m, 2H); 4.11 (dd, 8Hz, 6Hz; 2H), 4.47 (m; 2H); 4.63 (m; 4H), 6.58 (d, 8 Hz; 2H), 7.04-7.25 (m; 20H), 7.46 (d, 9Hz; 2H), 7.77 (d, 8Hz; 2H), 7.83 (d, 8Hz; 2H).

Example 16

N,N'-bis-(L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

100 mg N,N'-bis-(tert.-butyloxycarbonyl-L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R<4R-diol (example 1) were treated for 30 min at RT with a mixture of 2 ml 5N HCl in dioxane and 1 ml HCl in methanol. The volatile components were removed i. vac., the residue was washed with ether and the substance was dried in a high vacuum.

Yield: 59 mg

MS (FAB): 793 $(M + H)^+$, 775.

Example 17

N,N'-bis-(L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S<4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 793 $(M + H)^+$, 775.

Example 18

N,N'-bis-(L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 793 $(M + H)^+$, 775

Example 19

N,N'-bis-(L-seryl-L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 14

MS (FAB): 967 $(M + H)^+$

Example 20

N,N'-bis-(L-seryl-L-phenylalanyl-L-valyl-2S,5S-diamino-1,6-diphenyl-hexane-3R,4S-diol dihydrochloride

Synthesis analogous to example 14

MS (FAB): 967 $(M + H)^+$

Example 21

Bis-(N-(l-phenylalanyl-L-valyl)-2S-amino-3-phenylpropyl)-amine-trihydrochloride

Synthesis analogous to example 22

MS (FAB): 776 $(M + H)^+$

Example 22

Bis-(N-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-2S-amino-3-phenylpropyl) amine

Synthesis analogous to example 6 from example 23

MS (FAB, Lil): 982 $(M + Li)^+$, 976 $(M + H)^+$

NMR (270 MHz, DMSO <D_6>): 0.81 (m, 12H); 1.29 (s, 18H); 1.89 (m, 2H); c. 2.45-2.98 (m, c. 12H); 3.97 (m, 2H); 4.05-4.25 (m, 4H); 7.03 (d, 9Hz, 2H); 7.10-7.31 (m, 20H); 7.65 (d, 8Hz, 2H); 7.84 (d, 8Hz, 2H)

Example 23

Bis-(N-(L-valyl)-2S-amino-3-phenylpropyl-amine trihydrochloride

Synthesis analogous to example 16 from example 24

MS (FAB): 482 $(M + H)^+$

Example 24

Bis-(N-(tert.-butoxycarbonyl-L-valyl)-2S-amino-3-phenylpropyl) amine

Synthesis analogous to example 16 from example 25.

MS (FAB): 682 $(M + H)^+$

NMR (270 MHz, DMSO <D_6>): 0.73 (d, 6Hz, 6H); 0.77 (d, 6Hz, 6H); 1.38 (s, 18H); 1.65 (s, 18H); 1.82 (m, 2H); 2.42-c. 2.53 (m, c. 4H); 2.64 (dd, 14Hz,

8Hz, 2H); 2.84 (dd, 14Hz, 6Hz, 2H); 3.68 (m, 2H); 3.93 (m, 2H); 6.50 (d, 9Hz, 2H); 7.12-7.28 (m, 10H); 7.62 (d, 8Hz, 2H)

Example 25

Bis-(N-tert.-butoxycarbonyl-2S-amino-3-phenylpropyl)-amine hydrochloride

9.6 g tert.-butoxycarbonyl-L-phenylalaninal together with 30.5 g NH_4OAc and 1.7 g $NaBH_3CN$ were dissolved in 300 ml methanol and stirred for 6 h at RT. The solution was acidified with HCl to pH < 2. The product precipitates. It was digested with diethyl ether and water, dried in a high vacuum, and a yield of 3.1 g was obtained.

MS (FAB): 484 $(M + H)^+$, 428, 372.

NMR (270 MHz; DMSO $<D_6$): 1.33 (s, 18H); 2.55-2.90 (m; 8H), 3.82 (m; 2H), 6.75 (m; 2H), 7.12-7.325 (m; 10H).

Example 26

N,N'-bis-(5S-amino-4S-hydroxy-7-methyl-ocanoyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 643 $(M + H)^+$, 625.

NMR (270 MHz; DMSO $<D_6>$): 0.92 (m; 12H), 1.43 (m; 4H), 1.60 (m; 4H), 1.74 (m; 2H), 2.15 (m, 2H), 2.26 (m; 2H), 2.72 (dd, 14Hz, 11Hz, 2H), 2.93 (m; 2H), 3.12 (dm; 2H), 3.44 (m; 4H), 4.03 (m; 2H), c. 4.85 (m; c. 4H), 7.13-7.38 (m; 20H), 7.82 (m; 6H), 8.13 (d, 9Hz; 2H).

Example 26a

N,N'-bis-(N-tert.-butoxycarbonyl-5S-amino-7-methyl-4S-(tert.-butyl-dimethyl-silyl)oxy-octanoyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

88.5 mg N,N'-bis-(tert.-butyloxycarbonyl-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol were treated with 2 ml 5N HCl in dioxane for 30 min at RT. The volatile components were removed i. vac. and the residue was dried in a high vacuum. The 2S,5S-diamino-1,6-diphenyl-hexane-3S,5S-diol dihydrochloride obtained was dissolved in 5 ml dry DMF together with 211 mg N-tert.-butyloxycarbonyl-5S-amino-7-methyl-4S-(tert.-butyl-dimethyl-silyl)-oxy-octanoic acid (synthesis from (5S)-5-<(1S)-1-(N-Boc-amino)-3-methylbutyl > dihydrofuran-2(3H)-on (A. H. Fray, et al., J Org. Chem. 51 (1986), 4828-4833) analogous to the preparation of 5-(t-Boc-amino)-4-<tert.-butyldimethylsilyl)-oxy>-6-(phenylmethyl)-hexanoic acid (B. E. Evans, et al., J. Org. Chem. 50 (1985), 4615-4625)), 72 mg HOBt and 28.5 µl NEM. At 0°C 101 mg EDAC were added. The solution was stirred 1 h at 0°C, then overnight at RT. The solvent was spun off, the residue was taken up in EA and extracted with $KHSO_4$ solution, $NaHCO_3$ solution and NaCl solution. After drying of the organic phase it was concentrated and the residue was purified by chromatography on silica gel (DCM/acetonitrile 5/1).

Yield: 129 mg

MS (FAB): 1093 $(M + H)^+$, 1071 $(M + H)^+$, 971, 871.

NMR (270 MHz, DMSO <D_6>): 0.02 (s; 6H), 0.08 (s; 6H), 0.77-0.93 (M; 30H), c. 1.1-1.4 (m; c. 6H), 1.45-1.63 (m; 4H), 1.91 (m; 2H), 2.02-2.16 (m; 2H), 2.67 (dd, 11Hz, 14Hz; 2H), 3.36 (m; 2H), 3.42-3.56 (m; 4H), 3.95 (m; 2H), 4.81 (d, 6Hz; 2H), 6.44 (d, 8Hz; 2H), 7.08-7.30 (m; 10H), 7.79 (d, 9Hz; 1H).

Example 27

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-3S,6S-diamino-1,8-di-(4-pyridyl)-octane-4R,5R-diol

Synthesis analogous to example 6 from 3S,6S-diamino-1,8-di-(4-pyridyl)-octane-4R,5R-diol tetrahydrochloride.

NMR (270 MHz, DMSO <D_6>): 0.85 (d, 6Hz, 12H); 1.20 (s, 18H); 1.66 (m, 2H); 1.78 (m, 2H); 2.00 (m, 2H); c. 2.48 (m, 4H); 2.98 (m, 2H); c. 3.31 (m, 2H); 4.08 (m, 2H); 4.19 (m, 2H); 4.30 (m, 2H); 4.68 (m, 2H); 7.01 (d, 8Hz, 2H); 7.10-7.30 (m, 14H); 7.62 (d, 8Hz, 2H); 7.74 (d, 8Hz, 2H); 8.43 (d, 4.8 Hz, 4H)

MS (FAB): 1023 $(M + H)^+$, 923, 823.

Example 27a

3S,6S-diamino-1,8-di-(4-pyridyl)octane-4R,5R-diol tetrahydro-chloride

Synthesis analogous to examples 2, 2b, 2c and 2e proceeding from 1,2R-5R,6-diepoxy-3,4-O-isopropylidene-3R,4R-diol and 4-picolyllithium.

NMR (270 MHz, DMSO <D_6>): 1.87-2.20 (m, 4H); 3.10 (m, 4H); 3.29 (m, 2H); 3.84 (d, 6Hz, 2H); c. 3.3-4.5 (br, c. 4H); 8.07 (d, 7Hz, 4H); 8.18 (m, 6H); 8.88 (d, 7Hz, 4H).

MS (FAB): 331 $(M + H)^+$

Example 28

N,N'-bis-(2S-<2S-amino-3-phenyl-propyl>-amino-3-methyl-butanoyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol tetrahydrochloride

Synthesis analogous to example 16.

MS (FAB): 765 $(M + H)^+$

Example 29

N,N'-bis-(2S-<2S-tert.-butoxycarbonylamino-3-phenyl-propyl>-amino-3-methyl-butanoyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

From 50 mg N,N'-bis-(tert.-butoxycarbonyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,5S-diol the protective groups were removed analogous to example 8. The resultant 2S,5S-diamino-1,6-diphenyl-hexane-3S,5S-diol dihydrochloride was dissolved in 5 ml dry DMF together with 70 mg 2S-(2S-tert.-butoxycarbonyl-amino-3-phenyl-propyl)-amino-3-methyl-butyric acid (synthesis by reductive coupling of tert.-butoxycarbonyl-L-phenylalaninal and L-valine methyl ester hydrochloride with $NaBH_3CN$ <R, F. Borch, et al., J. Am. Chem. Soc. 93 (1971), 2897-2904> followed by customary methyl ester splitting), 41 mg HOBt and 12.6 µg NEM. 57 mg EDAC were added at 0°C. The solution was stirred for 1 h at 0°C and overnight at RT. The DMF was removed i. vac., the residue was taken up in DCM and washed with $KHSO_4$, $NaHCO_3$ and NaCl solutions. After drying and concentrating, the residue was triturated with diethyl ether.

Yield: 33 mg

MS (FAB): 965 $(M + H)^+$, 865, 765

NMR (270 MHz; DMSO <D_6>): 0.74 (d, 7Hz, 6H); 0.78 (d, 6Hz, 6H); 1.33 (s, 18H); 1.63 (m, 2H); 1.94-2.16 (m, 4H); c. 2.5 (m, c. 4H); 2.64 (m, 2H); 2.81 (dd, 14Hz, 5Hz, 2H); 3.13 (dm, 14Hz, 2H); 3.42 (m, 2H); 3.56 (m, 2H); 4.10 (m, 2H); 4.90 (m, 2H); 6.58 (d, 9Hz, 2H); 7.05-7.30 (m, 20H); 7.85 (d, 8Hz, 2H)

Example 30

N,N'-bis-(L-phenylalanyl-L-valyl)-2R,5R-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 793 $(M + H)^+$

Example 31

N,N'-bis-(L-phenylalanyl-L-valyl)-2R,5R-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 793 $(M + H)^+$

Example 32

N,N'-bis-(L-phenylalanyl-L-valyl)-2R,5R-diamino-1,6-diphenyl-hexane-3R,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 793 $(M + H)^+$

Example 33

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-2R,5R-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 6.

MS (FAB): 993 $(M + H)^+$, 893,793

NMR (270 MHz, DMSO <D_6>): 0.48 (d, 7Hz, 6H); 0.54 (d, 6Hz, 6H); 1.25 (s, 18H); 1.70 (m, 2H); 2.60 (t, 13Hz, 2H); 2.74 (dd, 14Hz, 11Hz, 2H); 2.96 (dd, 13Hz, 4Hz, 2H); 3.13 (dm, 14Hz, 2H); 3.39 (m, 2H); 4.02-4.25 (m, 6H); 4.88 (d, 4Hz, 2H); 7.02 (d, 9Hz, 2H), 7.07-7.33 (m, 20H); 7.60 (d, 9Hz, 2H); 8.24 (d, 9Hz, 2H).

Example 34

N,N-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-2R,5R-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 6.

MS (FAB): 993 $(M + H)^+$, 893, 793.

Example 35

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-2R,5R-diamino-1,6-diphenyl-hexane-3R,4S-diol

Synthesis analogous to example 6.

MS (FAB): 993 $(M + H)^+$, 893, 793.

Examples 36-38

36) N,N'-bis-(tert.-butoxycarbonyl)-2R,5R-diamino-1,6-diphenyl-hexane-3R,4R-diol

37) N,N'-bis-(tert.-butoxycarbonyl)-2R,5R-diamino-1,6-diphenyl-hexane-3S,4S-diol

38) N,N'-bis-(tert.-butoxycarbonyl)-2R,5R-diamino-1,6-diphenyl-hexane-3R,4S-diol

Synthesis analogous to examples 3-5 from tert.-butoxycarbonyl-D-phenylalaninal. The MS and NMR data correspond to those of their enantiomorphs from examples 3-5.

Example 39

N,N'-bis-(L-(1-naphthyl)alanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

Synthesis analogous to example 16

MS (FAB, LiI): 899 $(M + Li)^+$, 893 $(M + H)^+$, 875.

Example 40

N,N'-bis-(tert.-butoxycarbonyl-L-(1-naphthyl)alanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 6.

MS (FAB): 1093 $(M + H)^+$, 993.

NMR (270 MHz, DMSO $<D_6>$): 0.76 (m, 12H); 1.23 (s, 18H); 1.89 (m, 2H); 2.60-2.87 (m, 4H); 3.12 (dd, 14Hz, 10Hz, 2H); c. 3.33 (m, 2H); 3.52 (dm, 4Hz, 2H); 4.16-4.35 (m, 4H); 4.44 (m, 2H); 4.70 (s, 2H); 7.00-7.27 (m, 12H); 7.37-7.44 (m, 4H); 7.46-7.68 (m, 8H); 7.79 (m, 2H); 7.92 (d, 8Hz, 2H); 8.13 (d, 8Hz, 2H).

Example 41

N,N'-bis-[(2-(2-hydroxyethyl-sulfonylmethyl)-3-phenylpropionyl)-L-valyl]-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 13.

MS (FAB): 1007 $(M + H)^+$

Example 42

N,N'-bis-[L-phenylalanyl-L-valyl]-2S,5S-diamino-1,6-dicyclohexyl-hexane-3R,4R-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 805 $(M + H)^+$, 787.

Example 43

N,N'-bis-[L-phenylalanyl-L-valyl]-2S,5S-diamino-1,6-dicyclohexyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 805 $(M + H)^+$, 787.

Example 44

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-dicyclohexyl-hexane -3R,4R-diol

Synthesis analogous to example 6.

MS (FAB): 1005 $(M+H)^+$, 987, 905, 805.

Example 45

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-dicyclohexyl-hexane-3S,4S-diol

Synthesis analogous to example 6.

MS (FAB): 1005 $(M+H)^+$, 987, 905, 805.

NMR (270 MHz, DMSO <D_6>): 0.86 (m, 12H); 0.99-1.67 (m, c. 24H); 1.28 (s, 18H); 1.74 (m, 2H); 1.98 (m, 2H); 2.75 (dd, 14Hz, 11Hz, 2H); 2.96 (dd, 14Hz, 4Hz, 2H); 3.23 (m, 2H); 3.89 (m, 2H); 4.13-4.25 (m, 2H); 4.42 (d, 5Hz, 2H); 7.02 (d, 8Hz, 2H); 7.13-7.32 (m, 20H); 7.69-7.81 (m, 4H).

Example 46

N,N'-bis-(tert.-butoxycarbonyl)-2S,5S-diamino-1,6-dicyclohexyl-hexane-3S,4S-diol

200 mg N,N'-bis-(tert.-butoxycarbonyl)-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol were dissolved in 25 ml acetic acid and hydrogenated with 100 mg platinum dioxide as catalyst for 18 h at 60°C and 120 bar. After filtering off the catalyst the solvent was removed i. vac. and the residue was recrystallized from ethanol/water.

Yield: 150 mg.

MS (FAB): 535 $(M+Na)^+$, 513 $(M+H)^+$, 413.

NMR (270 MHz, DMSO <D_6>): 0.75 (m, 2H); 0.94 (m, 2H); 1.03-1.32 (m, 10H); 1.38 (s, 18H); 1.44 (m, 2H); 1.50-1.73 (m, 8H); 1.80 (m, 2H); 3.22 (m, 2H); 3.53 (m, 2H); 4.28 (d, 6Hz, 2H); 6.48 (d, 9Hz, 2H).

Example 47

N,N'-bis-(tert.-butoxycarbonyl)-2S,5S-diamino-1,6-dicyclohexyl-hexane-3R,4R-diol

Synthesis analogous to example 46.

MS (FAB): 513 $(M+H)^+$, 413.

NMR (270 MHz, DMSO <D_6>): 0.65-0.96 (m, 4H); 1.03-1.28 (m, 10H); 1.30-1.45 (m, 20H); 1.54-1.70 (m, 8H); 1.82 (m, 2H); 3.11 (m, 2H); 4.22 (m, 2H); 5.88 (d, 9Hz, 2H).

Example 48

N,N'-bis-(tert.-butoxycarbonyl)-2S,5S-diamino-1,6-dicyclohexyl-hexane-3R,4S-diol

Synthesis analogous to example 46.

MS (FAB): 513 $(M+H)^+$, 413.

Example 49

N,N'-bis-(4Z-aminocyclohexanecarbonyl-L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-3S,5S-diol dihydrochloride

Synthesis analogous to example 16 or 6.

MS (FAB): 1043 $(M+H)^+$, 1025.

Example 50

N,N'-bis-(4Z-N-tert.-butoxycarbonylamino)-cyclohexanecarbonyl-L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-3S,5S-diol dihydrochloride

Synthesis analogous to example 6.

MS (FAB): 1243 $(M+H)^+$, 1143, 1043.

Example 51

N,N'-bis-<(2S-(1,2-dimethylethyl-sulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 13.

MS (FAB): 1131 $(M+H)^+$, 716.

NMR (270 MHz, DMSO <D6>): 0.77 (d, 7Hz, 6H); 0.80 (d, 7Hz, 6H); 1.12 (s, 18H); 1.87 (m, 2H); 2.75 (m, 2H); 2.83 (m, 2H); 2.92-3.03 (m, 2H); 3.10-3.22 (m, 2H); c. 3.27-3.49 (m, 6H); 3.54-3.67 (m, 2H); 4.02-4.15 (m, 4H); 4.66 (d, 6Hz, 2H); 7.01-7.09 (m, 2H); 7.10-7.25 (m, 8H); 7.28-7.43 (m, 4H); 7.48-7.68 (m, 6H); 7.79 (d, 8Hz, 2H); 7.88-7.95 (m, 2H); 8.15-8.25 (m, 4H).

Example 52

N,N'-bis-<(2S-(1,1-dimethylethyl-sulfonylmethyl)-3-phenylpropionyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 13.

MS (FAB): 1053 $(M+Na)^+$, 1031 $(M+H)^+$

NMR (270 MHz, DMSO <D6>): 0.72 (d, 7Hz, 6H); 0.78 (d, 7Hz, 6H); 1.14 (s, 18H); 1.85 (m, 2H); 2.62-2.94 (m, 8H); c. 3.20-3.25 (m, c. 4H); 3.53 (dd, 10Hz, 14Hz, 2H); 4.02-4.13 (m, 2H); 4.50 (m, 2H); 4.64 (m, 2H); 7.01-7.10 (m, 2H); 7.12-7.39 (m, 22H); 8.05 (d, 8Hz, 2H).

Example 53

N,N'-bis-<(3-(1,1-dimethylethyl-sulfonyl)-propionyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 13.

MS (FAB): 873 $(M+Na)^+$, 851 $(M+H)^+$.

NMR (270 MHz, DMSO <D6>): 0.69 (d, 6Hz, 6H); 0.73 (d, 6Hz, 6H); 1.33 (s, 18H); 1.84 (m, 2H); 2.54-2.59 (m, 6H); 2.67 (m, 2H); c. 3.15-3.30 (m, 6H); 4.05 (dd, 7Hz, 9Hz, 2H); 4.47 (m, 2H); 4.63 (m, 2H); 7.06-7.21 (m, 10H); 7.30 (d, 9Hz, 2H); 7.94 (d, 8Hz, 2H).

Example 54

N,N'-bis-<(2R-(1,1-dimethylethyl-sulfonylmethyl)-3-(2-thienyl)-propionyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 13.

MS (FAB): 1065 $(M+Na)^+$, 1049 $(M+Li)^+$

NMR (270 MHz, DMSO<D6>): 0.51 (d, 7Hz, 6H); 0.56 (d, 7Hz, 6H); 1.28 (s, 18H); 1.85 (m, 2H); 2.95-3.19 (m, 8H); 3.30-3.60 (m, 8H); 3.95 (dd, 8Hz, 5.2Hz, 2H); 4.06 (m, 2H); 4.62 (d, 7Hz, 2H); 6.93 (d, 3.2Hz, 4H); 7.08-7.25 (m, 10H); 7.34 (m, 2H); 7.43 (d, 8.4Hz, 2H); 8.14 (d, 8Hz, 2H).

Example 55

N,N'-bis-(<L-phenylalanyl-L-valyl)-4S,7S-diamino-2,9-dimethyl-decane-5,6-diol dihydrochloride

Synthesis analogous to example 16 from example 56.

MS (FAB): 725 $(M+H)^+$

Example 56

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-4S,7S-diamino-2,9-dimethyl-decane-5,6-diol dihydrochloride

Synthesis analogous to example 6 or examples 3-5.

MS (FAB): 925 $(M+H)^+$, 826, 725

NMR (270 MHz, DMSO <D6>): 0.75-0.95 (m, 24H); 1.29 (s, 18H); 1.35-1.45 (m, 4H); 1.56 (m, 2H); 1.99 (m, 2H); 2.74 (dd, 10Hz, 13H, 2H); 2.95 (dd, 4Hz, 13Hz, 2H); 3.23 (m, 2H); 3.88 (m, 2H); 4.13-4.28 (m, 4H); 4.45 (d, 5Hz, 2H); 7.02 (8d, 8Hz, 2H); 7.13-7.33 (m, 10H); 7.76 (d, 8Hz, 2H), 7.80 (d, 8Hz, 2H).

Example 57

N,N'-bis-<(2S-(1,1-dimethylethyl-sulfonylmethyl)-3-phenylpropionyl)-L-valyl>-4S,7S-diamino-2,9-dimethyl-decane-3,4-diol

Synthesis analogous to example 13 or examples 3-5.

MS (FAB): 985 $(M+Na)^+$, 963 $(M+H)^+$

NMR (270 MHz, DMSO <D6>): 0.78 (d, 7Hz, 6H); 0.80-0.93 (m, 18H); 1.15 (s, 18H); 1.20-1.68 (m, 6H); 1.98 (m, 2H); 2.58 (dd, 10Hz, 14Hz, 2H); 2.73 (dd, 14Hz, 3Hz, 2H); 2.98 (dd, 14Hz, 4Hz, 2H); 3.23 (m, 2H); c. 3.33 (m, 2H); 3.47-3.61 (m, 2H); 3.85 (m, 2H); 4.14 (m, 2H); 4.44 (d, 5Hz, 2H); 7.15-7.33 (m, 10H); 7.69 (d, 9Hz, 2H); 8.22 (d, 9Hz, 2H).

Example 58

N,N'-bis-<(2-pyridyl)-acetyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

74 mg 2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydro-chloride and 68 mg 2-pyridyl acetyl hydrochloride were dissolved in 2 ml DMF, and 53 mg HOBt, 125 mg TBTU and 0.221 ml diisopropyl-ethylamine were added. The solution was stirred for 2 h at RT and worked up as usual. After chromatography on silica gel (DCM/MeOH 95/5 to 90/10) 68 mg of product were obtained.

MS (FAB): 759 $(M+Na)^+$, 737 (M+H)

NMR (270 MHz, DMSO <D6>): 0.70 (2d, 12H); 1.88 (m, 2H); 2.62 (dd, 14Hz, 5Hz, 2H); 2.77 (dd, 14Hz, 10Hz, 2H); 3.72 (m, 4H); 4.13 (dd, 6Hz, 9Hz, 2H); 4.46 (m, 2H); 7.05-7.23 (m, 10H); 7.28-7.40 (m, 4H); 7.48 (d, 9Hz, 2H); 7.82 (dt, 8Hz, 2H); 7.97 (d, 9Hz, 2H); 8.54 (m, 2H).

Example 59

N,N'-bis-<(4-pyridyl-thio)-acetyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

74 mg 2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride and 66 mg 4-pyridylmercaptoacetic acid were dissolved in 2 mg DMF, and 53 mg HOBt, 125 mg TBTU and 0.177 ml diisopropylamine were added. The solution was stirred for 2 h at RT, the solvent was removed i. vac. and the residue was stirred for 30 min between EA and $NaHCO_3$ solution. The insoluble part was filtered off and washed with EA and water. The raw product was dissolved in warm DMF, the solution filtered and stirred in EA. The precipitate was suctioned off and dried. Yield: 76 mg.

MS (FAB): 801 $(M+H)^+$

NMR (270 MHz, DMSO <D6>): 0.68 (2d, 12H); 1.84 (m, 2H); 2.62 (dd, 14Hz, 5Hz, 2H); 2.78 (dd, 14Hz, 9Hz, 2H); 3.28 (m, 2H); 3.73 (d, 15Hz, 2H); 3.90 (d, 15Hz, 2H); 4.17 (dd, 6Hz, 9Hz, 2H); 4.43 (m, 2H); 4.70 (m, 2H); 7.05-720 (m, 10H); 7.30 (m, 4H); 7.58 (d, 9Hz, 2H); 8.03 (d, 9Hz, 2H); 8.34 (m, 4H).

Example 60

N,N'-bis-<L-phenylalanyl-D-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 793 $(M+H)^+$

Example 61

N,N'-bis-<D-phenylalanyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 793 $(M+H)^+$

Example 62

N,N'-bis-<tert.-butoxycarbonyl-L-phenylalanyl-D-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 6.

MS (FAB): 993 $(M+H)^+$, 893, 793.

NMR (270 MHz, DMSO <D6>): 0.42 (d, 7Hz, 6H); 0.47 (d, 7Hz, 6H); 1.26 (s, 18H); 2.58 (m, 2H); 2.73 (m, 2H); 2.98 (dd, 13Hz, 5Hz, 2H); 3.16 (m, 2H);

3.40 (m, 2H); 4.00-4.32 (m, 6H); 4.85 (d, 5Hz, 2H); 6.86 (d, 9Hz, 2H); 7.07-7.30 (m, 20H); 7.74 (d, 9Hz, 2H); 8.19 (d, 9Hz, 2H).

Example 63

N,N'-bis-<tert.-butoxycarbonyl-D-phenylalanyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 6.

MS (FAB): 1015 $(M+Na)^+$, 993 $(M+H)^+$, 893, 793

NMR (270 MHz, DMSO <D_6>): 0.72 (d, 7Hz, 12Hz); 1.30 (s, 18H); 1.84 (s, 2H); 2.65-2.82 (m, 4H); 2.88-3.02 (m, 4H); 3.37 (m, 2H); 4.00-4.13 (m, 4H); 4.28 (m, 2H); 4.63 (d, 7Hz, 2H); 6.96 (d, 8Hz, 2H); 7.05-7.35 (m, 20H); 7.59 (d, 8Hz, 2H); 7.82 (d, 9Hz, 2H).

Example 64

N,N'-bis-<L-phenylalanyl-glycyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16

MS (FAB): 709 $(M+H)^+$.

Example 65

N,N'-bis-<L-phenylalanyl-L-isoleucyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 821 $(M+H)^+$

Example 66

N,N'-bis-<L-leucyl-glycyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 20.

MS (FAB): 641 $(M+H)^+$

Example 67

N,N'-bis-<tert.-butoxycarbonyl-L-phenylalanyl-glycyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S diol

Synthesis analogous to example 6.

MS (FAB): 931 $(M+Na)^+$, 909 $(M+H)^+$, 809, 709

NMR (270 MHz, DMSO <D_6>): 1.38 (s, 18H); 2.58-2.78 (m, 4H); 2.92-3.09 (m, 4H); 3.43-3.62 (m, 4H); 3.78 (dd, 16Hz, 5Hz, 2H); 4.05 (m, 2H); 4.19 (m, 2H); 4.83 (d, 5Hz, 2H); 6.92 (d, 9Hz, 2H); 7.10-7.29 (m, 10H); 7.90 (d, 9Hz, 2H); 8.01 (m, 2H).

Example 68

N,N'-bis-<tert.-butoxycarbonyl-L-phenylalanyl-L-isoleucyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 6.

MS (FAB): 1021 $(M+H)^+$, 921, 821

NMR (270 MHz, DMSO <D_6>): 0.70-0.85 (m, 12H); 1.03 (m, 2H); 1.29 (s, 18H); 1.37 (m, 2H); 1.65 (m, 2H); 2.68-2.80 (m, 4H); 2.84-3.04 (m, 4H); 3.39 (m, 2H); 4.00-4.13 (m, 4H); 4.20 (m, 2H); 4.64 (d, 7Hz, 2H); 7.02 (d, 9Hz, 2H); 7.05-7.33 (m, 20H); 7.62-7.73 (m, 4H).

Example 69

N,N'-bis-<tert.-butoxycarbonyl-L-leucyl-glycyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 6.

MS (FAB): 863 $(M+Na)^+$, 841 $(M+H)^+$, 741, 641

NMR (270 MHz, DMSO <D_6>): 0.83 (d, 6Hz, 6H); 0.87 (d, 6Hz, 6H); 1.38 (s, 18H); c. 1.42 (m, 4H); 1.60 (m, 2H); 2.62 (dd, 14Hz, 10Hz, 2H); 3.03 (dm, 14Hz, 2H); 3.44 (m, 2H); 3.52 (dd, 16Hz, 5Hz, 2H); 3.72 (dd, 16Hz, 5Hz, 2H); 3.90-4.08 (m, 4H); 4.79 (d, 5Hz, 2H); 6.93 (d, 9Hz, 2H); 7.10-7.28 (m, 10H); 7.78-7.90 (m, 4H).

Example 70

N,N'-bis-<L-phenylalanyl-L-seryl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 769 $(M+H)^+$

Example 71

N,N'-bis-<5S-amino-4S-hydroxy-7-methyl-2R-propyl-octanoyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

56 mg 2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride and 134 mg N-tert.-butoxycarbonyl-5S-amino-7-methyl-2R-propyl-4S-(tert.-butyl-dimethylsilyl-oxy)-octanoic acid were dissolved in 3 ml DMF, and 43 mg HOBt, 101 mg TBTU and 155 mg diisopropylethylamine were added. The solution was stirred for 4 h at RT, the solvent was removed i. vac. and the residue was divided between DCM and water. The organic phase was extracted with $KHSO_4$

solution, $NaHCO_3$ solution and water. After drying over anhydrous sodium sulfate the solution was concentrated and the residue was chromatographed on silica gel (cyclohexane/EA 3/1). The yield obtained was 157 mg N,N'-bis-<N-tert.-butoxycarbonyl-5S-amino-7-methyl-2R-propyl-4S-(tert.-butyldimethylsilyl-oxy)-actanoyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride. Treatment with HCl in dioxane analogous to example 16 yielded the product.

The coupling component N-tert.-butoxycarbonyl-5S-amino-7-methyl-2R-propyl-4S-(tert.-butyldimethylsilyl-oxy)-octanoic acid was prepared analogous to the description in example 27.

For this, the initial material (5S)-5-<(1S)-1-(N-Boc-amino)-3-methylbutyl>dihydrofuran-2(3H)-on was additionally alkylated with allyl bromide and then hydrogenated (analogous to the preparation of compound 11 in Fray, et al.).

MS (FAB): 727 $(M+H)^+$

NMR (270 MHz, DMSO <D6>): 0.80-0.88 (m, 18H); 1.08-1.74 (m, 18H); c. 2.55 (m, 2H); 2.72-2.88 (m, 4H); 3.02-3.18 (m, 4H); 3.48 (d, 7Hz, 2H); 3.99 (m, 2H); 7.10-7.19 (m, 2H); 7.20-7.32 (m, 10H); 7.74 (m, 6H); 8.16 (d, 9Hz, 2H).

Example 72

N,N'-bis-<L-phenylalanyl-L-cyclohexylglycyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 873 $(M+H)^+$

Example 73

N,N'-bis-<tert.-butoxycarbonyl-L-phenylalanyl-L-cyclohexylglycyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 6

MS (FAB): 1073 $(M+H)^+$, 973, 873

NMR (270 MHz, DMSO <D_6>): 0.82-1.66 (m, c. 22H); 1.29 (s, 18H); 2.56-2.97 (m, 8H); c. 3.30 (m, 2H); 4.08-4.22 (m, 4H); 4.50 (m, 2H); 4.63 (m, 2H); 7.02 (d, 9Hz, 2H); 7.04-7.32 (m, 20H); 7.47 (d, 9Hz, 2H); 7.56 (d, 9Hz, 2H).

Example 74

N,N'-bis-<L-methionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 761 $(M+H)^+$

Example 75

N,N'-bis-<tert-butoxycarbonyl-L-methionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 6.

MS (FAB): 961 $(M+H)^+$, 861, 761

NMR (270 MHz, DMSO <D_6>): 0.75 (d, 6Hz, 12H); 1.38 (s, 18H); 1.70-1.90 (m, 6H); 2.02 (s, 6H); c. 2.37-2.5 (m, 4H); c. 3.32 (m, 2H); 3.94-4.10 (m, 6H); 4.63 (d, 7Hz, 2H); 7.04-7.20 (m, 12H); 7.49-7.59 (m, 4H).

Example 76

N,N'-bis-<(O-methyl-tyrosyl)-L-valyl>2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 853 $(M+H)^+$

Example 77

N,N'-bis-<tert.-butoxycarbonyl-(O-methyl-tyrosyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 16.

MS (FAB): 1053 $(M+H)^+$, 953, 853

NMR (270 MHz, DMSO <D_6>): 0.73-0.83 (m, 12H); 1.29 (s, 12H); 1.84 (m, 2H); 2.60-3.02 (m, 8H); 3.36 (m, 2H); 3.70 (s, 6H); 4.64 (d, 6Hz, 2H); 6.82 (d, 9Hz, 4H); 6.98 (d, 9Hz, 2H); 7.05-7.22 (m, 14H); 7.59 (d, 9Hz, 2H); 7.65 (d, 9Hz, 2H).

Example 78

N,N'-bis-<L-tyrosyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 825 $(M+H)^+$

Example 79

N,N'-bis-<(N-tert.-butoxycarbonyl-O-tert.-butyl-L-tyrosyl)-L-valyl>-2S,5S-diamino-1,,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 6.

MS (FAB): 1137 $(M+H)^+$, 1037, 937

NMR (270 MHz, DMSO <D_6>): 0.72-0.85 (m, 12H); 1.25 (s, 18H); 1.28 (s, 18H); 1.85 (m, 2H); 2.62-2.82 (m, 4H); 2.84-3.01 (m, 4H); 3.36 (m, 2H); 3.98-4.12 (m, 4H); 4.19 (m, 2H); 4.64 (d, 7Hz, 2H); 6.85 (d, 8Hz, 4H); 7.02 (d, 9Hz, 2H); 7.05-7.21 (m, 18H); 7.60 (d, 8hz, 2H); 7.66 (d, 9hz, 2H).

Example 80

N,N'-bis-<N^6-benzyloxycarbonyl-N^2-(tert.-butoxycarbonyl-L-lysyl)-L-valyl>2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 6.

MS (FAB/Lil): 1229 $(M+H)^+$

Example 81

N,N'-bis-<N^6-benzyloxycarbonyl-N^2-(tert.-butoxycarbonyl-L-phenylalanyl)-L-lysyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 6.

MS (FAB): 1319 $(M+H)^+$, 1219, 1185

NMR (270 MHz, DMSO <D6>): 1.08-1.47 (m, 30H); 2.60-2.82 (m, 6H); 2.87-3.00 (m, 6H); 3.23 (m, 2H); 4.08-4.23 (m, 4H); 4.36 (m, 2H); 4.69 (m, 2H); 4.99 (s, 4H); 6.94 (d, 9Hz, 2H); 7.04-7.40 (m, 32H); 7.46 (d, 8Hz, 2H); 7.69 (d, 9Hz, 2H).

Example 82

N,N'-bis-<L-glutamyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB/LiI): 763 $(M+Li)^+$, 757 $(M+H)^+$

NMR (270 MHz, DMSO <D_6>): 0.81 (d, 6Hz, 6H); 0.85 (d, 6Hz, 6H); 0.78-1.98 (m, 6H); 2.20-2.38 (m, 4H); 2.76 (m, 2H); 2.97 (m, 2H); c. 3.35 (m, c. 2H); 3.89 (m, 2H); 4.01-4.14 (m, 4H); 4.68 (d, 7Hz, 2H); 7.06-7.21 (m, 10H); 7.68 (d, 8Hz, 2H); 8.22 (m, 6H); 8.46 (d, 9Hz, 2H).

Example 83

N,N'-bis-<tert.-butoxycarbonyl-L-glutamyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis from example 84 by catalytic hydrogenation on Pd/carbon in glacial acetic acid/water 9/1.

MS (FAB): 979 $(M+Na)^+$, 958 $(M+H)^+$

NMR (270 MHz, DMSO <D_6>): 0.70-0.82 (m, 12H); 1.38 (s, 18H); 1.62-1.93 (m, 6H); 2.17-2.29 (m, 4H); 2.74 (m, 2H); 2.95 (dm, 13Hz, 2H); c. 3.35 (m, 2H); 3.90-4.09 (m, 6H); 4.12 (m, 2H); 7.00-7.20 (m, 12H); 7.48-7.62 (m, 4H).

Example 84

N,N'-bis-<(N-tert.-butoxycarbonyl-O-benzyl-L-glutamyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 6.

MS (FAB): 1159 $(M+Na)^+$, 1137 $(M+H)^+$, 1037

NMR (270 MHz, DMSO <D_6>): 0.75 (d, 6Hz, 18H); 1.37 (s, 18H); 1.70-1.98 (m, 6H); 2.33-2.45 (m, 2H); 2.76 (m, 2H); 2.93 (m, 2H); c. 3.3 (m, 2H); 3.94-4.08 (m, 6H); 4.60 (s, 7Hz, 2H); 5.08 (s, 4H); 7.03-7.17 (m, 12H); 7.30-7.48 (m, 10H); 7.50 (d, 8Hz, 2H); 7.58 (d, 9Hz, 2H).

Example 85

N,N'-bis-<glycyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 635 $(M+Na)^+$, 613 $(M+H)^+$

Example 86

N,N'-bis-<tert.-butoxycarbonyl-glycyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 6.

MS (FAB): 835 $(M+Na)^+$, 813 $(M+H)^+$

NMR (270 MHz, DMSO <D_6>): 0.70 (d, 7Hz, 12H); 1.38 (s, 18H); 1.84 (m, 2H); 2.62 (dd, 14Hz, 4Hz, 2H); 2.87 (dd, 14Hz, 10Hz, 2H); 3.26 (m, 2H); 3.52 (d, 6Hz, 4H); 4.13 (m, 2H); 4.42 (m, 2H); 4.69 (m, 2H); 7.03 (m, 2H); 7.08-7.21 (m, 10H); 7.38 (d, 9Hz, 2H); 7.50 (d, 9Hz, 2H).

Example 87

N,N'-bis-<L-leucyl-L-valyl>=2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 747 $(M+Na)^+$, 725 $(M+H)^+$

Example 88

N,N'-bis-<tert.-butoxycarbonyl-L-leucyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 6.

MS (FAB): 947 $(M+Na)^+$, 925 $(M+H)^+$, 825, 725

NMR (270 MHz, DMSO <D_6>): 0.72-0.80 (m, 12H); 0.85 (d, 7Hz, 6H); 0.89 (d, 7Hz, 6H); 1.28-1.54 (m, 22H); 1.60 (m, 2H); 1.81 (m, 2H); 2.76 (dd, 13Hz, 9Hz, 2H); 2.93 (dd, 13Hz, 4Hz, 2H); c. 3.33 (m, 2H); 3.92-4.09 (m, 6H); 4.60 (d, 7Hz, 2H); 7.04 (d, 8Hz, 2H); 7.05-7.20 (m, 10H); 7.48 (d, 9Hz, 4H).

Example 89

N,N'-bis-<L-(S-dioxo)methionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 847 $(M+Na)^+$, 825 $(M+H)^+$

Example 90

N,N'-bis-<tert.-butoxycarbonyl-L-(S-dioxo)methionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R-4R-diol

Synthesis analogous to example 6.

MS (FAB): 1074 $(M+Na)^+$

NMR (270 MHz, DMSO <D_6>): 0.65-0.78 (m, 12H); 1.39 (s, 18H); 1.74-2.07 (m, 6H); 2.63 (m, 2H); 2.78 (m, 2H); 3.07 (m, 4H); 3.26 (m, 2H); 3.98-4.17 (m, 4H); 4.44 (m, 2H); 4.67 (m, 2H); 7.07-7.23 (m, 12H); 7.49 (d, 9Hz, 2H); 7.53 (d, 9Hz, 2H).

Example 91

N,N'-bis-<(2S-(1,1-dimethylethyl-sulfonylmethyl)-3-phenylpropionyl)-L-tert.-butylglycyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 13.

MS (FAB): 1081 $(M+Na)^+$, 1059 $(M+H)^+$

NMR (270 MHz, DMSO <D_6>): 0.83 (s, 18H); 1.12 (s, 18H); 2.39 (dd, 11Hz, 14Hz, 2H); 2.56-2.72 (m, 4H): 2.73-2.90 (m, 4H); c. 3.25-3.40 (m, c. 4H); 3.53 (dd, 10Hz, 2H); 4.20 (d, 9Hz, 2H); 4.54 (m, 2H); 4.62 (m, 2H); 6.98 (m, 2H); 7.07-7.36 (m, 18H); 7.47 (d, 9Hz, 2H); 7.98 (d, 9Hz, 2H).

Example 92

N,N'-bis-<(2S-(1,1-dimethylethyl-sulfonylmethyl)-3-phenylpropionyl)-L-neopentylglycyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 13.

MS (FAB): 1109 $(M+Na)^+$, 1087 $(M+H)^+$

NMR (270 MHz, $CDCl_3$): 0.86 (s, 18H); 1.08 (dd, 8Hz, 14Hz, 2H); 1.35 (s, 18H); 1.58 (dd, 14Hz, 4Hz, 2H); 2.75-3.45 (m, c. 8H); 3.80 (m, 2H); 4.12 (m, 2H); 5.80 (d, 8Hz, 2H); 6.27 (d, 8Hz, 2H); 7.10-7.36 (m, c. 10H).

Example 93

N,N'-bis-<(2-S-hydroxy-3-phenylpropionyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Added to 0.065 mmol N,N'-bis-<-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol hydrochloride and 33 mg S-phenyl lactic acid in 4 ml DMF were 27 mg HOBt, 64 mg TBTU and then, slowly, 0.088 ml diisopropylethylamine. After 15 min at RT the DMF was removed in a vacuum, the residue was taken up in EA and extracted with $KHSO_4$ solution, $NaHCO_3$ solution and water. The organic phase was dried with $MgSO_4$ and concentrated, the residue was triturated with ether and suctioned off.

Yield: 43 mg.

MS (FAB): 795 $(M+H)^+$

NMR (270 MHz, DMSO <D_6>): 0.63 (d, 7Hz, 6H); 0.67 (d, 7Hz, 6H); 1.82 (m, 2H); 2.64-2.79 (m, 4H); 2.91-3.04 (m, 4H); 3.38 (m, 2H); 3.97-4.17 (m, 6H); 4.72 (d, 6Hz, 2H); 5.77 (d, 6Hz, 2H); 7.08-7.29 (m, 20H); 7.38 (d, 9Hz, 2H); 7.85 (d, 8Hz, 2H).

Example 94

N,N'-bis-<(2S-hydroxy-4-phenylbutyryl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

Synthesis analogous to example 93

MS (FAB): 845 $(N+Na)^+$, 823 $(M+H)^+$

NMR (270 MHz, DMSO <D_6>): 0.73 (d, 5Hz, 6H); 0.76 (d, 5Hz, 6H); 1.76-2.00 (m, 6H); 2.55-2.78 (m, 6H); 2.98 (dm, 14Hz, 2H); 3.39 (m, 2H); 3.89 (m, 2H); 4.00-4.18 (m, 4H); 4.75 (d, 6Hz, 2H); 5.88 (d, 6Hz, 2H); 7.05-7.32 (m, 20H); 7.45 (d, 9Hz, 2H); 7.88 (d, 8Hz, 2H).

Example 95

N,N;-bis-<(2-(1-imidazolylmethyl)-3-phenyl-propionyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol (from "diastereomer 1")

35.8 mg 2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-dioldihydro-chloride were dissolved with 90 mg 2-(1-imidazolyl-methyl)-3-phenyl-propionyl-L-valine ("diastereomer 1") in 2 ml DMF, and 32 mg HOBt, 77 mg TBTU and subsequently 0.163 ml diisopropylethylamine were added at RT. The solution was stirred for 3 h, the solvent was removed i. vac. and the residue was divided between EA and $NaHCO_3$ solution. The organic phase was washed with semi-concentrated NaCl solution, dried and concentrated. The residue was triturated with diethyl

ether, suctioned off and then chromatographed on silica gel (EA/MeOH 85/15). 57 mg of product were obtained.

MS (FAB): 923 $(M+H)^+$

The preparation of the 2-(1-imidazolylmethyl)-3-phenylpropionyl-L-valine proceeded as follows: 1.53 g benzylacrylic ester (J. Med. Chem. 31, 1839, (1988)) and 550 mg imidazole were dissolved in 30 ml EtOH and, under argon at room temperature, 40 mg NaH were added. After 7 days the reaction solution was poured into 50 ml KH_2PO_4 solution and extracted three times with 50 ml methyl-tert.-butyl ether. The organic phase was extracted twice with $NaHSO_4$, the aqueous phase was adjusted alkaline with K_2CO_3 and again extracted twice with 50 ml methyl-tert.-butyl ether. After concentration one obtains 390 mg 2-benzyl-3-(1-imidazolyl)propionic ethyl ester. This was saponified with NaOH and coupled with valine methyl ester according to the PPA method. The diastereomers were separated with EA/MeOH 10/1.

0.34 = diastereomer 1

0.18 = diastereomer 2

Saponification with NaOH in dioxane/water led to the coupling components for examples 95 and 96.

Example 96

N,N'-bis-<(2-(1-imidazolylmethyl)-3-phenyl-propionyl)-L-valyl>2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol (from "diastereomer 2")

For preparation see example 95.

MS (FAB): 923 $(M+H)^+$

Example 97

N,N'-bis-<3-(4-amino-1-piperidyl-sulfonyl)-2-benzylpropionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 16.

MS (FAB): 1115 $(M+H)^+$

Example 98

N,N'-bis-<2-benzyl-3-(4-tert.-butoxycarbonyl-amino-1-piperidyl-sulfonyl)-propionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol.

57 mg N,N'-bis-<L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride and 129 mg 2-benzyl-3-(4-tert.-butoxy-carbonyl-amino-1-piperidyl-sulfonyl)-propionic acid were dissolved in 1 ml DMF, and 41 mg HOBt, 96 mg TBTU and 135 µl diisopropylethylamine were added. After 20 min the solvent was removed i. vac., the residue was taken up in DCM and extracted with $KHSO_4$ solution, $KHCO_3$ solution and water. After drying and concentrating, the viscous residue was dissolved in a little DCM/MeOH and precipitated with diethyl ether. Yield: 64 mg.

MS (FAB): 1337 $(M+Na)^+$, 1315 $(M+H)^+$, 1237, 1215, 1137, 1115

2-benzyl-3-(4-tert.-butoxycarbonyl-amino-1-piperidylsulfonyl)-propionic acid was synthesized analogous to example 13 according to: J. Med. Chem. 31 1839 (1988). The intermediate stage of the benzylacrylic ester was converted with thioacetic acid to 3-acetylthio-2-benzylpropionic benzyl ester. Subsequent oxidation with chlorine produced 2-benzyl-3-chlorosulfonyl-propionic benzyl ester was converted into the coupling component above by coupling with 4-tert.-butoxycarbonylamino-piperidine subsequent hydrogenation.

Example 99

N,N'-bis-<3-(4-amino-1-piperidyl-carbonyl)-2R-benzylpropionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R<4R-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 1043 $(M+H)^+$

Example 100

N,N'-bis-<2R-benzyl-3-(4-tert.-butoxycarbonyl-amino-1-piperidyl-carbonyl)-propionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

57 mg N,N'-bis-<L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride and 129 mg 2R-benzyl-3-(4-tert.-butoxycarbonyl-amino-1-piperidyl-carbonyl)-propionic acid (synthesis by coupling of 4-tert.-butoxycarbonylamino-piperidine to 2-R-benzyl-3-carboxypropionic benzyl ester <see literature reference in example 102>) were dissolved in 1 ml DMF, and 41 mg HOBt, 96 mg TBTU and then, slowly, 0.135 ml diethylisopropylamine were added. After 20 min the solvent was removed i. vac., the residue was taken up in EA and extracted with $KHSO_4$ solution, $NaHCO_3$ solution and water. The organic phase was dried over $MgSO_4$ and concentrated. The residue was dissolved in a little DCM, precipitated with diethyl ether and filtered off. Yield: 64 mg.

MS (FAB): 1265 $(M+Na)^+$, 1243 $(M+H)^+$

Example 101

N,N'-bis-<(2R-benzyl-3-carboxyl)-propionyl-L-valyl>2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis from example 102 by treatment with trifluoroacetic acid.

MS (FAB): 901 $(M+Na)^+$, 879 $(M+H)^+$

Example 102

N,N'-bis-<(2R-benzyl-3-tert.-butoxycarbonyl)-propionyl-L-valyl>-2S,5S-diamino-hexane-3R,4R-diol

45 mg N,N'-bis-<valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride together with 75 mg 2R-benzyl-3-tert.-butoxycarbonyl-propionic acid were dissolved in 2 ml DMF, and 37 mg HOBt, 87 mg TBTU and 112 µl ethyldiisopropylamine were added. The solution was stirred for 15 min at RT, the DMF was removed i. vac., the residue was taken up in EA an extracted with $KHSO_4$ solution, $NaHCO_3$ solution and water. The organic phase was dried over $MgSO_4$ and concentrated. The residue was triturated with diethyl ether and filtered off.

Yield: 44 mg.

MS (FAB): 1013 $(M+Na)^+$, 991 $(M+H)^+$

NMR (270 MHz, DMSO <D_6>): 0.69 (d, 6Hz, 6H); 0.74 (d, 6Hz, 6H); 1.31 (s, 18H); 1.83 (m, 2H); 1.95 (m, 2H); 2.32-2.47 (m, 4H); 2.60-2.87 (m, 6H); 2.98 (m, 2H); 3.29 (m, 2H); 4.09 (dd, 8Hz, 7Hz, 2H); 4.46 (m, 2H); 4.64 (m, 2H); 7.02-7.31 (m, 10H); 7.38 (d, 9Hz, 2H); 7.80 (d, 8Hz, 2H).

The preparation of the carboxy-protected succinic acid derivative in enantiomer-pure form was carried out according to Evans (D. A. Evans, et al., J. Am. Chem. Soc. 104, 1737 (1982); J. J. Plattner, et al., J. Med. Chem. 31, 2277 (1988).

Example 103

N,N'-bis-<(3-amino-2-benzyl)-propionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride (from "diastereomer 1")

Synthesis analogous to example 16 from example 105.

MS (FAB): 843 $(M+Na)^+$, 821 $(M+H)^+$

Example 104

N,N'-bis-<(3-amino-2-benzyl)-propionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride (from "diastereomer 2")

Synthesis analogous to example 16 from example 106.

MS (FAB): 843 $(M+Na)^+$, 821 $(M+H)^+$

Example 105

N,N'-bis-<(2-benzyl-3-tert.-butoxycarbonyl-amino)-propionyl-L-valyl>-2S,5S-1,6-diphenyl-hexane-3R,4R-diol (from "diastereomer 1")

37 mg 2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-dioldihydro-chloride were coupled with 98 mg N,N'-bis-(2-benzyl-3-tert.-butoxycarbonyl-amino)-propionyl-L-valine according to the TBTU method. After the usual working up and chromatography 28 mg of product were obtained.

MS (FAB): 1043 $(M+Na)^+$ 1021 $(M+H)^+$, 921, 821

The building block N,N'-bis-(2-benzyl-3-tert.-butoxycarbonyl-amino)-propionyl-L-valine was prepared as follows. 2.3 g sodium were dissolved in 170 ml EtOH and 32 ml cyanoacetic ethyl ester were added. 11.5 ml benzylchloride were added by drops with stirring. The solution stood overnight at RT. The NaCl was filtered off and the solvent was distilled off.

The residue was dissolved in EA and extracted with H_2O. The organic phase was concentrated, the residue was distilled i. vac. (0.5 mm Hg/120-125°C).
Yield: 8.1 g.

The benzylcyanoacetic ethyl ester obtained was dissolved in 200 ml EtOH and hydrogenated over Raney nickel. After suctioning off the catalyst and concentrating, 8.2 g of oil were obtained; after chromatography over silica gel (EA after EA/MeOH 5/1), 5.5 g of 3-amino-2-benzylpropionic ethyl ester.

This compound was reacted with Boc_2O to 2-benzyl-3-(tert.-butoxycarbonylamino)-propionic ethyl ester, saponified and coupled with H-Val-OMe according to the PPA method. The diastereomers obtained were separated by chromatography (toluene/diisopropyl ether 1/1).

Rf = 0.140 = diastereomer 1

Rf = 0.097 = diastereomer 2

Saponification with NaOH in dioxane/water led to the coupling components for examples 105 and 106.

Example 106

N,N'-bis-<(2R-benzyl-3-tert.-butoxycarbonyl-amino)-propionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol (from "diastereomer 2")

Synthesis analogous to example 105.

MS (FAB): 1043 $(M+Na)^+$, 1021 (M+H), 921, 821

Example 107

N,N'-bis-<O-(D-mannofuranosyl)-2S-hydroxy-3-phenyl-propionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

20 mg of the compound from example 108 were stirred for 30 min with methanolic hydrochloric acid at RT. The volatile components were distilled off i. vac., the residue was digested with diethyl ether, suctioned off and dried.

Yield: 13 mg.

NMR (270 MHz, DMSO <D_6>): 0.58 (d, 6Ha, 6H); 0.62 (d, 6Hz, 6H); 1.82 (m, 2H); 2.60 (dd, 4Hz, 14Hz, 2H); 2.71-2.82 (m, 4H); 2.98 (dd, 14Hz, 3Hz, 2H); c. 3.25 (m, 2H); 3.30-3.49 (m, 6H); 3.58 (m, 2H); 3.67 (dd, 11Hz, 3Hz, 2H); c. 3.70-4.30 (m, c. 16H); 4.43 (m, 2H); 4.49 (m, 2H); 7.05-7.29 (m, 20H); 7.35 (d, 9Hz, 2H); 7.67 (d, 9Hz, 2H).

Example 107a

N,N'-bis-<O-(2,3-5,6-diisopropylidene-D-mannofuranosyl)-2S-hydroxy-3-phenyl-propionyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

57 mg N,N'-bis-<L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride were dissolved with 90 mg O-(2,3-5,6-diisopropylidene-D-mannofuranosyl)-2S-hydroxy-3-phenylpropionic acid in 1 ml DMF and coupled with the TBTU method. Yield: 60 mg.

MS (FAB): 1279 $(M+H)^+$, 1261, 1221

NMR (270 MHz, DMSO <D_6>): 0.63 (d, 6Hz, 6H); 0.69 (d, 6Hz, 6H); 1.19 (s, 6H); 1.21 (s, 6H); 1.30 (s, 12H); 1.79 (m, 2H); 2.60-2.82 (m, 8H); 3.29 (m, 2H); 3.73 (dd, 9Hz, 6Hz, 2H); 3.85-3.98 (m, 4H); 4.01-4.18 (m, 4H); 4.23 (dd, 8Hz, 3Hz, 2H); 4.40 (d, 6Hz, 2H); 4.45 (m, 2H); 4.62-4.72 (m, 4H); 7.03-7.32 (m, c. 22H); 7.40 (d, 9Hz, 2H); 7.59 (d, 9Hz, 2H).

O-(2,3-5,6-diisopropylidene-D-mannofuranosyl)-2S-hydroxy-3-phenyl-propionic acid was prepared according to R. R. Schmidt from 2,3-5,6-

diisopropylidene-D-mannofuranose and 2S-hydroxy-3-phenyl-propionic acid (R. R. Schmidt and I. Michel; Angew. Chem. 92, 763 (1980); Angew. Chem. Int. Ed. Engl. 19, 731 (1980).

405 mg O-(2,3-5,6-diisopropylidene-D-mannofuranosyl-trichloroacetimidate together with 194 mg phenyl lactic ethyl ester were dissolved in 15 ml abs. CH_2Cl_2. The solution was cooled to 0°C and 100 µl of a 1M BF_3 etherate solution in CH_2Cl_2 was added. The solution was permitted to stand for 1 h at 0°C, was poured into 100 ml $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic phase was dried with Na_2SO_4 and concentrated. After chromatography with silica gel (mobile solvent: methyl tert.-butyl ether/heptane (1/1)) 195 mg of product were obtained.

Example 108

N,N'-bis-(L-phenylalanyl-L-valyl)-3S,6S-diamino-1,8-di(4-pyridyl)-octane-4R,5R-diol tetrahydrochloride

Synthesis analogous to example 16 from 27

MS (FAB): 823 $(M+H)^+$

Example 109

N,N'-bis-<N-(ß-D-1-deoxylfructose-1-yl)-L-phenylalanyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol diacetate

69 mg N,N'-bis-<L-phenylanalyl-L->valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride were suspended with 79 mg D-glucose in 6 ml MeOH and 2 ml pyridine and boiled for 4.5 h. The solvent was removed i. vac., the residue was separated by chromatography over Sephadex LH20 with 10% aqueous acetic acid.

Yield: 71 mg.

MS (FAB): 1139 $(M+Na)^+$, 1117 $(M+H)^+$

Example 110

N,N'-bis-<D-gluconyl-L-phenylalanly-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis: treatment of the compound from example 111 with ammonia-saturated methanol.

MS (FAB): 1171 $(M+Na)^+$

Example 111

N,N'-bis-<2,3,4,5,6-penta-O-acetyl-D-gluconyl-L-phenylalanyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis: by coupling of 2,3,4,5,6-pent-O-acetyl-D-gluconic acid (C. E. Braun and C. D, Cook, Organic Synthesis, vol. 5, 887-889 (1973)) to N,N'-bis-<L-phenylalanly-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride with the TBTU method.

MS (FAB): 1569 $(M+H)^+$

Example 112

N-N'-bis-<tert.-butoxycarbonyl-L-phenylalanyl-L-valyl>-1,4-diamino-butane-2R,3R-diol

Synthesis analogous to example 6 from 1,4-diamino-butane-2R,3R-diol dihydrochloride.

NMR (270 MHz, DMSO <D_6>): 0.83 (d, 6Hz, 12H); 1.31 (s, 18H); 1.93 (m, 2H); 2.73 (m, 2H); 2.91-3.07 (m, 4H); 3.28 (m, 2H); 3.42 (m, 2H); 4.18 (m,

4H); 4.57 (m, 2H); 7.02 (d, 8Hz, 2H); 7.13-7.32 (m, 10H); 7.66 (d, 8.4Hz, 2H); 8.04 (m, 2H).

MS (FAB): 835 $(M+Na)^+$, 813 $(M+H)^+$, 713, 613

Example 112a

1,4-diamino-butane-2R,3R-diol dihydrochloride

Synthesis from (+)-1,4-di-O-tosyl-2.3-O-isopropylidene-D-threitol analogous to examples 2, 2b and 2c.

NMR (60 MHz, DMSO <D_6>): 2.9 (m, 4H); 3.73 (m, 2H); c. 5.7-4.5 (br, c. 2H); 8.1 (m, c. 6H).

MS (DCI): 121 $(M+H)^+$, 104

Example 113

N,N'-bis-<L-phenylalanyl-L-valyl>-1,4-diamino-butane-2R,3R-diol dihydrochloride

Synthesis analogous to example 16 from 112.

MS (FAB): 635 $(M+Na)^+$, 613 $(M+H)^+$

Example 114

N,N'-bis<tri-benzyloxycarbonyl-L-arginyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane 3R,4R-diol

NMR (270 MHz, DMSO <D_6>): 0.71 (d, 7Hz, 12H); 1.57 (m, 8H); 1.80 (m, 2H); 2.73 (m, 2H); 2.94 (m, 2H); 3.30 (m, 2H); 3.70-4.12 (m, 10H); 4.58 (d, 7Hz, 2H); 4.92-5.18 (m, 8H); 5.19 (s, 4H); 7.00-7.42 (m, 40H); 7.49 (d, 8Hz, 4H); 7.64 (d, 8.4Hz, 2H); 9.13 (br.s, 4H).

Example 115

N,N'-bis-<tert.-butyloxycarbonyl-L-cyclohexylalanyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 6.

MS (FAB): 1005 $(M+H)^+$, 905

NMR (270 MHz, DMSO <D_6>): 0.67 (d, 7Hz, 6H); 0.80 (d, 7Hz, 6H) 0.80-1.84 (m, 26H); 1.42 (s, 18H); 2.13 (sept., 7Hz, 2H); 2.80 (dd, 15Hz, 9Hz, 2H); 3.35 (m, 4H); 4.03 (m, 4H); 4.30 (qd, 9Hz, 4Hz, 2H); 4.96 (d, 4Hz, 2H); 6.57 (d, 8Hz, 4H); 7.10-7.30 (m, 12H).

Example 116

N,N'-bis-<L-cyclohexylalanyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

Synthesis analogous to example 16.

MS (FAB): 805 $(M+H)^+$, 553, 531

NMR (270 MHz, DMSO <D_6>): 0.79 (d, 7Hz, 6H); 0.85 (d, 7Hz, 6H); 1.00-1.95 (m, 28H); 2.77 (dd, 14Hz, 7Hz, 2H); 2.93 (m, 2H); 3.37 (m, 2H); 3.89 (m, 2H); 4.09 (m 4H); 4.70 (d, 7Hz, 2H); 7.16 (m, 10H); 7.66 (d, 8Hz, 2H); 8.17 (s, 6H); 8.47 (d, 9Hz, 2H).

Example 117

N,N'-bis-<benzyloxycarbonyl-L-tryptophyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 6.

MS (FAB): 1139 $(M+H)^+$, 720

NMR (270 MHz, DMSO <D_6>): 0.75 (m, 12H); 1.96 (m, 2H); 2.76 (dd, 13Hz, 7Hz, 2H); 2.90-3.13 (m, 6H); 3.40 (m, 2H); 4.07 (m, 4H); 4.38 (m, 2H); 4.65 (d, 7Hz, 2H); 4.88 (d, 14Hz, 2H); 4.97 (d, 14Hz, 2H); 6.90-7.35 (m, 28H); 7.47 (d, 8Hz, 2H); 7.58 (d, 8Hz, 2H); 7.65 (d, 8Hz, 2H); 7.83 (d, 8Hz, 2H); 10.80 (s, 2H).

Example 118

N,N'-bis-<L-tryptophyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 11.

MS (FAB): 871 $(M+H)^+$

NMR (270 MHz, DMSO <D_6>): 0.75 (m, 12H); 1.88 (m, 2H); 2.75 (m, 4H); 2.98 (dd, 14Hz, 2Hz, 2H); 3.13 (dd, 14Hz, 3Hz, 2H); 3.42 (m, 2H); 3.73 (m, 2H); 4.10 (m, 4H); 4.73 (d, 6Hz, 2H); 6.09-7.24 (m, 18H); 7.35 (d, 8Hz, 2H); 7.63 (d, 8Hz, 2H); 7.80 (d, 8Hz, 2H), 8.22 (s, 6H); 10.90 (s, 2H).

Example 119

N,N'-bis-<benzyloxycarbonyl-L-1,2,3,4-tetrahydro-isoquinoline-3-yl-carbonyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 6.

MS (FAB): 1107 $(M+Na)^+$, 1085 $(M+H)^+$

NMR (270 MHz, DMSO <D_6>): 0.55 (m, 12); 1.70 (m 2H); 2.60-3.81 (m, 10H); 3.90 (m, 2H); 4.03 (m, 2H); 4.38-4.80 (m, 8H); 4.91-5.20 (m, 4H); 7.00-7.53 (m, 28H); 7.58 (d, 8Hz, 2H); 7.72 (d, 8Hz, 2H).

Example 120

N,N'-bis-<L-1,2,3,4-tetrahydro-isoquinoline-3-yl-carbonyl-L-valyl>2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol diacetate

Synthesis analogous to example 11.

MS (FAB): 839 $(M+Na)^+$, 817 $(M+H)^+$

NMR (270 MHz, DMSO <D_6>): 0.70 (d, 7Hz, 12H); 1.86 (m, 2H); 1.92 (s, 6H); 2.64-2.89 (m, 4H); 2.92 (dd, 16Hz, 5Hz, 2H); 3.02 (dd, 13Hz, 3Hz, 2H); 3.39 (m, 2H); 3.47 (dd, 9Hz, 5Hz, 2H); 3.90 (s, 4H); 4.03 (m, 2H); 4.10 (dd, 9Hz, 5Hz, 2H); 4.74 (br.s, 2H); 7.02-7.26 (m, 18H); 7.77 (m, 18H); 7.85 (d, 8Hz, 2H).

Example 121

N,N'-bis-<(2-(benzyl-sulfinyl-methyl)-3-phenyl-propionyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 13.

Synthesis of the building block (2-(benzyl-sulfinyl-methyl)-3-phenyl-propionic acid was accomplished analogous to literature: J. Med. Chem. 3, 1839 (1988).

MA (FAB): 1089 $(M+Na)^+$, 1067 $(M+H)^+$, 710

NMR (270 MHz, DMSO <D_6>): 0.45 (m, 6H); 0.72 (m, 6H); 1.80 (m, 2H); 2.53-2.95 (m, 12H); 3.22-3.36 (m, 4H); 3.55 (m, 2H); 3.73-4.26 (m, 6H); 4.48 (m, 2H); 7.00-7.40 (m, 30H); 7.85-8.07 (m, 4H).

Example 122

N,N'-bis-<(2-(p-chlorobenzyl-thio-methyl)-3-phenyl-propionyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 13.

Synthesis of the building block (2-(p-chlorobenzyl-thio-methyl)-3-phenyl-propionic acid was accomplished analogous to literature: J. Med. Chem. 31, 1839 (1988).

MS (FAB): 1125 $(M+Na)^+$

NMR (270 MHz, DMSO <D_6>); 0.49 (m, 6H); 0.57 (m, 6H); 1.80 (m, 2H); 2.10-2.33 (m, 2H); 2.38-2.60 (m, 4H); 2.62-2.83 (m, 6H); 2.95 (m, 2H); 3.28 (m, 2H); 3.65 (s, 4H); 4.03-4.17 (m, 2H); 4.45 (m, 2H); 4.54-4.67 (m, 2H); 7.00-7.50 (m, 28H); 7.64 (m, 2H); 7.88 (m, 2H).

Example 123

N,N'-bis-<(2-(p-chlorobenzyl-sulfonyl-methyl)-3-phenylpropionyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 13.

Synthesis of the building block 2-(p-chlorobenzyl-sulfonyl-methyl)-3-phenyl-propionic acid was accomplished analogous to literature: J. Med. Chem. 31, 1839 (1988).

MS (FAB): 1191 $(M+2H+Na)^+$ 1189 $(M+Na)^+$

NMR (270 MHz, DMSO <D_6>): 0.52 (m, 6H); 0.74 (m, 6H); 1.83 (m, 2H); 2.42-2.95 (m, 10H); 3.28-3.54 (m, 6H); 3.90-4.70 (m, 10H); 6.98-7.47 (m, 30H); 8.03 (m, 2H)

Example 124

N,N'-bis-<N-tosyl(-β-naphthyl-alanyl-L-valyl>2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 6.

MS (FAB): 1223 $(M+Na)^+$

NMR (270 MHz, DMSO <D_6>): 0.66 (m, 12H); 1.80 (m, 2H); 2.13 (s, 6H); 2.50-2.90 (m, 8H); 3.30 (m, 2H); 3.98-4.67 (m, 8H); 6.70-8.00 (m, 38H).

Example 125

N,N'-bis-<N-mesyl-ß-naphthyl-alanyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 6.

MS (FAB): 1072 $(M+Na)^+$, 838

NMR (270 MHz, <D_6>): 0.74 (m, 12H); 1.82 (s, 6H); 1.87 (m, 2H); 2.55-3.08 (m, 8H); 3.25 (m, 2H); 4.02 (m, 2H); 4.22 (m, 2H); 4.47 (m, 2H); 4.70 (m, 2H); 7.00-8.00 (m, 30H).

Example 126

N-<(2R-(1,1-dimethylethyl-sulfonylmethyl)-3-phenylpropionyl)-L-valyl>-N'-<(2S-1,1-dimethylethylsulfonylmethyl)-3-phenyl-propionyl)-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Byproduct from the synthesis of example 52.

Example 126 Rf = 0.17 (EA)

Example 52 Rf = 0.35 (EA)

MS (FAB): 1053 $(M+Na)^+$

NMR (270 DMSO <D_6>): 0.47 (d, 7Hz, 3H); 0.48 (d, 7Hz, 3H); 0.70 (d, 7Hz, 3H); 0.75 (d, 7Hz, 3H); 1.14 (s, 9H); 1.27 (s, 9H); 1.82 (m, 2H); 2.60-3.00 (m, c. 10H); 3.08-3.35 (m, c. 3H); 3.38-3.58 (m, 3H); 3.91 (dd, 8Hz, 6Hz, 1H); 4.06 (m, 1H); 4.27 (d, 5Hz, 1H); 4.35-4.54 (m, 3H); 7.00-7.38 (m, 22H); 7.93 (d, 8Hz, 2H); 8.04 (d, 8Hz, 2H).

The following compounds of examples 127-134 were obtained analogous to the syntheses as described in examples 6 or 16.

Example 127

N,N'-bis-<tert.-butoxycarbonyl-L-valyl>-2R,5R-diamino-1,6-diphenyl-hexane-3R,4R-diol

MS (FAB): 699 $(M+H)^+$, 599, 499

Example 128

N,N'-bis-<tert.-butoxycarbonyl-L-valyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

MS (FAB, LiI): 717 $(M+Li)^+$

Example 129

N,N'-bis-<tert.-butoxycarbonyl-L-cyclohexylglycine>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

MS (FAB): 801 $(M+Na)^+$, 779 $(M+H)^+$, 679

Example 130

N,N'-bis-<tert.-butoxycarbonyl-L-asparaginyl>-2S,5S-diamino-1,6-diophenyl-hexane-3R,4R-diol

MS (FAB): 729 $(M+H)^+$, 629

Example 131

N,N'-via-<L-valyl>-2S,5S-diamino-1,6-dicyclohexyl-hexane-3S,4S-diol dihydrochloride

Example 132

N,N'-bis-<N^6-benzoxycarbonyl-L-lysyl>-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

Example 133

N,N'-bis-<glycyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol dihydrochloride

MS (FAB): 415 $(M+H)^+$

Example 134

N,N-bis-<tert.-butoxycarbonyl-glycyl>-2S,5S-diamino-1,6-diphenyl-hexane-3S,4S-diol

MS (FAB): 615 $(M+H)^+$

The following compounds of examples 135-140 were obtained analogous to the syntheses as contained in examples 23 or 24.

Example 135

Bis-<N-((N^2-tert.-butoxycarbonyl-L-lysyl)-L-leucyl)-2S-amino-3-phenyl-propyl>-amine trihydrochloride

MS (FAB): 966 $(M+H)^+$

Example 136

Bis-<N-(tert.-butoxycarbonyl-2S-amino-3-cyclohexyl-propyl>-amine hydrochloride

MS (FAB): 495 $(M+H)^+$

Example 137

Bis-<N-(L-leucyl)-2S-amino-3-phenyl-propyl>-amine trihydrochloride

MS (FAB): 510 $(M+H)^+$

Example 138

Bis-<N-(tert.-butoxycarbonyl-L-leucyl)-2S-amino-3-phenylpropyl>-amine

MS (FAB): 710 $(M+H)^+$

Example 139

Bis-<2S-amino-3-phenyl-propyl>-amine trihydrochloride

MS (FAB): 284 $(M+H)^+$

Example 140

Bis-<N-(benzyloxycarbonyl-L-valyl)-2S-amino-3-phenyl-propyl> amine

MS (FAB): 750 $(M+H)^+$

Example 141

Bis-<N-tert.-butoxycarbonyl-2S-amino-3-methyl-butyl>-amine hydrochloride

Synthesis analogous to example 25.

MS (FAB); 388 $(M+H)^+$

Example 142

N,N'-bis-<(2S-(1,1-dimethylethyl-sulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl>-3S,6S-diamino-1,8-di-(4-pyridyl)-octane-4R<5R diol

Synthesis analogous to example 13 from 27a.

NMR (270 MHz, DMSO $<D_6>$): 0.83 (m, 12H); 1.14 (s, 18H); 1.66 (m, 2H); 1.82 (m, 2H); 2.00 (m, 2H); 2.50-2.78 (m, 4H); 2.86 (m, 2H); 3.06-3.63 (m,

10H); 4.02 (m, 2H); 4.14 (m, 2H); 4.69 (m, 2H); 7.30-7.60 (m, 14H); 7.74 (d, 8Hz, 2H); 7.87 (m, 2H); 8.16 (m, 2H); 8.32 (d, 8Hz, 2H); 8.58 (m, 4H).

MS (FAB): 1161 $(M+H)^+$

Example 143

N,N'-bis-<(2S-(1,1-dimethylethyl-sulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl>-1,4-diamino-butane-2R,3R-diol

Synthesis analogous to example 13 from 112a.

NMR (270 MHz, DMSO <D_6>): 0.82 (d, 6Hz, 12H); 1.17 (s, 18H); 1.92 (m, 2H); 2.92-3.08 (m, 4H); 3.16-3.53 (m, 10H); 3.53 (dd, 12.8Hz, 8.8Hz, 2H); 4.11 (dd, 8.0Hz, 7.2Hz, 2H); 4.55 (d, 4.8Hz, 2H); 7.38-7.67 (m, 10H); 7.80 (m, 2H); 7.92 (m, 2H); 8.12 (d, 8.4Hz, 2H); 8.20 (d, 8Hz, 2H).

MS (FAB): 973 $(M+Na)^+$; 951 $(M+H)^+$

Example 144

N,N'-bis-<tert.-butoxycarbonyl-L-phenylalanyl-L-valyl>-1,4-diamino-butane

Synthesis analogous to example 6.

NMR (270 MHz, DMSO <D_6>): 0.83 (d, 6Hz, 12H); 1.28 (s, 18H); 1.39 (m, 4H); 1.91 (m, 2H); 2.74 (dd, 12.8Hz, 9.6Hz, 2H); 2.89-3.16 (m, 6H); 4.08-4.23 (m, 4H); 7.02 (d, 8Hz, 2H); 7.14-7.30 (m, 10H); 7.63 (d, 8.4Hz, 2H); 7.95 (m, 2H).

MS (FAB): 781 $(M+H)^+$, 681, 581

Example 145

N,N'-bis-<l-phenylalanyl-L-valyl>-1,4-diamino-butane dihydrochloride

Synthesis analogous to example 16 from 144.

MS (FAB): 581 $(M+H)^+$

Example 146

N,N'-bis-<(2S-(1,1-dimethylethyl-sulfonylmethyl)-3-(1-naphthyl)-propionyl)-L-valyl>-1,4-diamino-butane

Synthesis analogous to example 13.

NMR (270 MHz, DMSO <D_6>): 0.82 (d, 6Hz, 12H); 1.19 (s, 18H); 1.32 (m, 4H); 1.89 (m, 2H); 2.98 (m, 4H); 3.32 (m, 2H); 3.42 (m, 6H); 3.54 (dd, 12.8Hz, 8Hz, 2H); 4.04 (t, J=8Hz, 2H); 7.38 (m, 4H); 7.53 (m, 6H); 7.79 (m, 2H); 7.92 (m, 2H); 8.08 (d, 8Hz, 2H); 8.21 (m, 2H).

MS (FAB): 941 $(M+Na)^+$, 919 $(M+H)^+$

Example 147

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-3S,5S-diamino-1,8-diphenyl-octane-4R,5R-diol

Synthesis analogous to example 6 from 3S,6S-diamino-1,8-diphenyl-octane-4R,5R-diol dihydrochloride (latter compound was prepared analogous to examples 2, 2b, 2c and 2e from 1,2R-5R,6-diepoxy-3,4-O-isopropylidene-3R,4R-diol and benzyl lithium).

MS (FAB (LiI)): 1027 $(M+Li)^+$, 927, 827

NMR (270 MHz, DMSO <D_6>): 0.88 (m, 12H); 1.28 (s, 18H); 1.57-1.86 (m, 4H); 2.01 (m, 2H); 2.4-2.6 (m, c. 4H); 2.75 (dd, 11Hz, 14Hz, 2H); 2.98 (dd, 14Hz, 4Hz, 2H); 3.32 (m, c. 2H); 4.06-4.26 (m, 4H); 4.32 (dd, 6Hz, 8Hz, 2H); 4.62 (m, 2H); 7.0 (d, 8Hz, 2H); 7.10-7.32 (m, 20H); 7.62 (d, 10Hz, 2H); 7.75 (d, 8Hz, 2H).

Example 148

N,N'-bis-(L-phenylalanyl-L-valyl)-3S,6S-diamino-1,8-diphenyl-octane-4R,5R-diol dihydrochloride

Synthesis analogous to example 16 from 147.

MS (FAB): 821 $(M+H)^+$, 843 $(M+Na)^+$, 803

Example 149

N,N'-bis-(<2S-(1,1-dimethylethyl-sulfonylmethyl)-3-(1-naphthyl)-propionyl>-L-valyl)-3S,6S-diamino-1,8-diphenyl-octane-4R,5R-diol

Synthesis analogous to examples 13 and 147.

MS (FAB (LiI)): 1165 $(M+Li)^+$

NMR (270 MHz, DMSO <D_6>): 0.92 (d, 7Hz, 12H); 1.13 (s, 18H; 1.6-1.85 (m, 4H); 2.04 (m, 2H); 2.40-2.64 (m, 4H); 2.82 (dm, 14Hz, 2H); 3.18 (m, 2H); 3.32-3.52 (m, 6H); 3.58 (m, 2H); 4.08 (m, 2H); 4.22 (t, 8Hz, 2H); 7.1-7.56 (m, 20H); 7.72 (dd, 4Hz, 2H); 7.88 (m, 2H); 8.14 (m, 2H); 8.32 (d, 8Hz, 2H).

Example 150

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-6S,9S-diamino-tetradecane-7R,8R-diol

Synthesis analogous to t example 6 from 6S,9S-diamino-tetradecane-7R,8R-diol dihydrochloride (latter compound was prepared analogous to examples 2, 2b, 2c and 2e from 1,2R-5R,6-diepoxy-3,4-O-isopropylidene-3R,4R-diol and n-butyl lithium).

MS (FAB(LiI)): 959 $(M+Li)^+$

NMR (270 MHz, DMSO <D_6>): 0.76-0.91 (m, 18H), 1.12-1.54 (m, 16H); 1.28 (s, 18H); 1.98 (m, 18H); 2.74 (dd, 12Hz, 14Hz, 2H); 2.87 (dd, 14Hz, 4Hz, 2H);

3.22 (m, 2H); 3.98 (m, 2H); 4.14-4.32 (m, 4H); 4.46 (s, 2H); 7.0 (d, 8Hz, 2H); 7.14-7.31 (d, 4Hz, 10H); 7.38 (d, 9Hz, 2H); 7.70 (d, 9Hz, 2H).

Example 161

N,N'-bis-(L-phenylalanyl-L-valyl)-6S,9S-diamino-tetradecane-7R,8R-diol dihydrochloride

Synthesis analogous to example 16 from 150.

MS (FAB): 753 $(M+H)^+$, 775 $(M+Na)^+$, 735

Example 152

N,N'-bis-(<2S-(1,1-dimethylethyl-sulfonylmethyl)-3-(naphthyl)-propionyl>-L-valyl)-6S,9S-diamino-tetradecane-7R,8R-diol

Synthesis analogous to examples 13 and 150.

MS (FAB (Lil)): 1097 $(M+Li)^+$

NMR (270 MHz, DMSO <D_6>): 0.76 (m, 6H); 0.88 (d, 7Hz, 12H); 1.12 (s, 18H); c. 1.10-1.54 (m, 16H); 2.02 (m, 2H); 2.82 (dd, 12Hz, 2Hz, 2H); 3.16 (dd, 12Hz, 16Hz, 2H); 3.24 (m, 2H); 3.36-3.52 (m, 4H); 3.58 (dd, 8Hz, 13Hz, 2H); 3.98 (m, 2H); 4.16 (t, 6Hz, 2H); 4.44 (s, 2H); 7.18 (d, 10Hz, 2H); 7.42-7.48 (m, 4H); 7.49-7.62 (m, 4H); 7.81 (m, 2H); 7.92 (m, 2H); 8.20 (d, 8Hz, 2H); 8.30 (d, 8.4Hz, 2H).

Example 153

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-valyl)-2S,5S-diamino-1,8-bis-(3,4-methylenedioxyphenyl)-hexane-3R,4R-diol

Synthesis analogous to example 6 from 2S,5S-diamino-1,6-bis-(3,4-methylenedioxyphenyl)-hexane-3R,4R-dio dihydrochloride (latter compound was

prepared analogous to examples 2, 2b, 2c and 2e from 1,2R-5R,6-diepoxy-3,4-O-isopropylidene-3R,4R-diol and 3,4-methylenedioxyphenyl lithium).

MS (FAB): 1103 $(M+Na)^+$, 1081 $(M+H)^+$

NMR (270 MHz, DMSO <D_6>): 0.73 (d, 6Hz, 6H); 0.76 (d, 6Hz, 6H); 1.28 (s, 18H); 1.87 (m, 2H); 2.52-2.78 (m, 6H); 2.91 (dd, 14Hz, 4Hz, 2H); 3.26 (m, 2H); 4.11-4.22 (m, 4H); 4.35 (m, 2H); 4.66 (m, 2H); 5.84 (s, 2H); 5.86 (s, 2H); 6.63 (d, 8Hz, 2H); 6.69 (d, 8Hz, 2H); 6.75 (s, 2H); 6.99 (d, 9Hz, 2H); 7.13-7.33 (m, 10H); 7.45 (d, 9Hz, 2H); 7.59 (d, 9Hz, 2H).

Example 154

N,N'-bis-(L-phenylalanyl-L-valyl)-2S,5S-diamino-1,6-bis-(3,4-methylenedioxyphenyl)-hexane-3R,4R-diol dihydrochloride

Synthesis analogous to example 16 from 153.

MS (FAB): 881 $(M+H)^+$, 863

Example 155

N,N'-bis-(<2S-(1,1-dimethylethyl-sulfonylmethyl)-3-(1-naphthyl)-propionyl>-L-valyl)-2S,5S-diamino-1,6-bis-(3,4-methylenedioxy-phenyl)-hexane-3R,4R-diol

Synthesis analogous to examples 13 and 153.

MS (FAB); 1241 $(M+Na)^+$, 1219 $(M+H)^+$

NMR (270 MHz, DMSO <D6>): 0.73 (d, 7Hz, 6H); 0.78 (d, 7Hz, 6H); 1.10 (s, 18H); 1.89 (m, 2H); 2.55-2.72 (m, 4H); 2.79 (dm, 14Hz, 2H); 3.08 (dd, 14Hz, 10Hz, 2H); c. 3.22-3.43 (m, c. 6H); 3.58 (dd, 14Hz, 10Hz, 2H); 4.07 (m, 2H); 4.45 (m, 2H); 4.49 (m, 2H); 5.75 (s, 2H); 5.78 (s, 2H); 6.68 (s, 2H); 6.80 (s. 2H); 7.25 (d, 9Hz, 2H); 7.39-7.45 (m, 4H); 7.54 (m, 6H); 7.80 (m, 2H); 7.92 (m, 2H); 8.15-8.25 (m, 4H).

Example 156

N,N'-bis-(<2S-(1,1-dimethylethyl-sulfonylmethyl)-3-(1-naphthyl)-propionyl>-L-isoleucyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 13.

MS (FAB): 1181 $(M+Na)^+$

NMR (270 MHz, DMSO <D_6>): 0.63 (d, 7Hz, 6H); 0.73 (t, 7Hz, 6H); 0.99 (m, 2H); 1.11 (s, 18H); 1.32 (m, 2H); 1.64 (m, 2H); 2.63-2.88 (m, 6H); 3.07 (dd, 15Hz, 11Hz, 2H); c. 3.28-3.43 (m, c. 6H); 3.58 (dd, 14Hz, 9Hz, 2H); 4.09 (t, 8Hz, 2H); 4.48-4.62 (m, 4H); 7.03 (m, 2H); 7.12-7.31 (m, 10H); 7.43 (m, 4H); 7.54 (m, 4H); 7.81 (m, 2H); 7.92 (m, 2H); 8.15-8.25 (m, 4H).

Example 157

N,N'-bis-(N^2-<hexadecyl-sulfonyl>-L-lysyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to examples 11 and 58.

MS (FAB): 1330 $(M+H)^+$

Example 158

N,N'-bis-(N^2-<tetradecanoyl>L-lysyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to examples 11 and 58.

MS (FAB): 1174 $(M+H)^+$

Example 159

N,N'-bis-(tert.-butoxycarbonyl-L-phenylalanyl-L-asparaginyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 6.

MS (FAB): 1045 $(M+Na)^+$

NMR (270 MHz, DMSO <D6>): 1.27 (s, 18H); 2.20-2.78 (m, 10H); 2.90 (m, 2H); 3.30 (m, 2H); 4.14 (m, 2H); 4.28 (m, 2H); 4.45 (m, 2H); 4.64 (s, 2H); 6.88 (s, 4H); 7.02-7.37 (m, 24H); 8.04 (d, 8Hz, 2H).

Example 160

N,N'-bis-(L-phenylalanyl-L-asparaginyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 16 from 159.

MS (FAB): 823 $(M+H)^+$

Example 161

N,N'-bis-(<2S-(1,1-dimethylethyl-sulfonylmethyl)-3-(naphthyl)-propionyl>L-asparaginyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 13.

MS (FAB): 1183 $(M+Na)^+$

NMR (270 MHz, DMSO <D_6>): 1.17 (s, 18H); 2.22 (m, 2H); 2.37-2.76 (m, 10H); 2.90 (m, 2H); 3.25 (m, 4H); 3.58 (m, 2H); 4.25 (m, 2H); 4.40 (m, 2H); 4.62 (m, 2H); 6.93-7.60 (m, 24H); 7.77 (m, 2H); 7.90 (m, 2H); 8.22 (d, 8Hz, 2H); 8.33 (d, 8Hz, 2H).

Example 162

N,N'-bis-(<2-(1,1-dimethylethyl-sulfonylmethyl)-3-(4-pyridyl)-propionyl>L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol dihydrochloride

Synthesis analogous to example 13.

2-(1,1-dimethylethyl-sulfonylmethyl)-3-(4-pyridyl)-propionic acid was used as racemate in the coupling; the diastereomer products were separated chromatographically.

Rf values: mobile solvent acetic ester/methanol/glacial acetic acid 60/40/1.

a) Rf = 0.50

b) Rf = 0.44

c) Rf = 0.33

MS (FAB):

a) isomer 1: 1055 $(M+Na)^+$ 1033 $(M+H)^+$

b) isomer 2: 1055 $(M+Na)^+$ 1033 $(M+H)^+$

c) isomer 3: 1055 $(M+Na)^+$

NMR (270 MHz, DMSO <D_6>):

a) isomer 1: 0.68 (d, 7Hz, 6H); 0.74 (d, 7Hz, 6H); 1.19 (s, 18H); 1.83 (m, 2H); 2.53-2.94 (m, 10H); c. 3.2-3.45 (m, c. 10H); 3.53 (dd, 14Hz, 9Hz, 2H); 4.06 (dd, 9Hz, 7Hz, 2H); 4.52 (m, 2H); 7.05 (m, 2H); 7.10-7.25 (m, 8H); 7.28 (d, 5Hz, 4H); 7.53 (d, 9Hz, 2H); 8.19 (d, 9Hz, 2H); 8.46 (d, 8Hz, 4H)

b) isomer 2: 0.38, 0.44, 0.65, 0.73 (d, each 7Hz, each 3H), 1.18, 1.28 (2s, each 9H); 1.70-1.88 (m, 2H); 2.54-3.05 (m, c. 11H); 3.15-3.60 (m, c. 10H); 3.87 (dd, 8Hz, 6Hz, 2H); 4.03 (dd, 9Hz, 7Hz, 1H); 4.36-4.52 (m, 2H); c. 4.4-5.0 (1H); 7.00-7.30 (m, 14H); 7.41, 7.58, 8.18, 8.27 (4d, each 9Hz, each 1H); 8.43, 8.46 (2d, each 6Hz, each 1H)

c) isomer 3: 0.34 (d, 7Hz, 6H); 0.40 (d, 7Hz, 6H); 1.31 (s, 18H); 1.73 (m, 2H); 2.60-3.07 (m, 12H); 3.28 (s, 2H); 3.38-3.58 (m, 4H); 3.81 (dd, 8Hz, 6Hz, 2H); 4.42 (m, 2H); c. 4.3-5.3 (2H); 7.03-7.30 (m, 14Hz), 7.43 (d, 9Hz, 2H); 8.28 (d, 9Hz, 2H); 8.43 (d, 6Hz, 4H).

Example 163

N,N'-bis-(<2-(1,1-dimethylethyl-sulfonylmethyl)-3-(N-oxido-4-propionyl>L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 162.

2-(1,1-dimethylethyl-sulfonylmethyl)-3-(N-oxido-4-pyridyl)-propionic acid comes from the preliminary stage 2-(1,1-dimethylethyl-thio-methyl)-3-(4-pyridyl)-propionic acid through oxidation with three instead of two equivalents of potassium peroxymonosulfate (Oxone^{R}) as in example 162.

MS (FAB): 1065 $(M+H)^+$

Example 164

N,N'-bis-(<bis-(1,1-dimethylethyl-thio-methyl)-acetyl>L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 13. The synthesis of the bis-(1,1-dimethylethyl-thio-methyl)-acetic acid was accomplished from bis-(hydroxymethyl)-maleic diethyl ester by reaction with hydrogen bromide and subsequent substitution of the ß,ß'-dibromoisobutyric acid with potassium tert.-butyl sulfide.

MS (FAB): 990 $(M+H)^+$

NMR (270 MHz, CDCl3): 0.59 (d, 7Hz, 6H); 0.85 (d, 7Hz, 6H); 1.29 (s, 18H); 1.33 (s, 18H); 2.16 (m, 2H); 2.42 (m, 2H); 2.70-3.02 (m, 14H); 3.48 (br.s, 2H); 4.13 (m, 2H); 4.28 (m, 2H); 5.33 (d, 8Hz, 2H); 6.47 (d, 8Hz, 2H); 7.20-7.28 (m, 10H).

Example 165

N,N'-bis-(<bis(-1,1-dimethylethyl-sulfonylmethyl)-acetyl>L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to examples 164 and 13.

MS (FAB): 1118 $(M+H)^+$

Example 166

N,N'-bis-(<1-naphthyl>-acetyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 58.

MS (FAB): 834 $(M+H)^+$

Example 167

N,N'-bis-(<1-naphthyloxy>-acetyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 58.

MS (FAB): 866 $(M+H)^+$

Example 168

N,N'-bis-(<2S-(1,1-dimethylethyl-sulfonylmethyl)-3-(1-naphthyl)-propionyl>L-valyl)-2S,5S-diamino-1,6-bis-(4-tert.-butylphenyl)-hexane-3R-4R-diol

Synthesis analogous to example 6 from 2S,5S-diamino-1,6-bis-(tert.-butylphenyl)-hexane-3R,4R-diol dihydrochloride (latter compound was prepared analogous to examples 2, 2b, 2c and 2e from 1,2-R-5R,6-diepoxy-3,4-O-isopropylidene-3R,4R-diol and 4-tert.-butylphenyl lithium).

MS (FAB): 1265 $(M+H)^+$

NMR (270 MHz, DMSO <D6>): 0.67 (d, 7Hz, 6H); 0.76 (d, 7Hz, 6H); 1.09 (s, 18H); 1.11 (s, 18H); 1.87 (m, 2H); 2.60-2.85 (m, 6H); 3.08 (dd, 14Hz, 12Hz, 2H); 3.25-3.50 (m, 8H); 3.60 (dd, 14Hz, 9Hz, 2H); 4.06 (m, 2H); 4.52 (m, 2H); 7.10-7.22 (m, 8H); 7.27 (d, 9Hz, 2H); 7.34-7.62 (m, 8H); 7.80 (m, 2H); 7.92 (m, 2H); 8.22 (d, 8Hz, 4H).

Example 169

N,N'-bis-(<2S-(1,1-dimethylethyl-sulfonylmethyl)-3-(1-naphthyl)-propionyl>L-valyl)-2S,5S-diamino-1,6-bis-(2,4-dimethoxyphenyl)-hexane-3R,4R-diol

Synthesis analogous to example 6 from 2S,5S-diamino-1,6-bis-(2,4-dimethoxyphenyl)-hexane-3R,4R-diol dihydrochloride (latter compound was prepared analogous to examples 2, 2b, 2c and 2e from 1,2R-5R,6-diepoxy-3,4-O-isopropylidene-3R,4R-diol and 2,4-dimethoxyphenyl lithium).

MS (FAB): 1250 $(M+H)^+$

Example 170

N,N'-bis-(2-<4-pyridyl>ethylsulfonyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 58.

MS (FAB): 836 $(M+H)^+$

Example 171

N,N'-bis-(12-amino-dodecanoyl-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 58.

MS (FAB): 892 $(M+H)^+$

Example 172

N,N'-bis-(<2-quinolylcarbonyl>-L-valyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 58.

MS (FAB): 831 $(M+Na)^+$, 809 $(M+H)^+$

NMR (270 MHz, DMSO <D6>): 0.80 (d, 7Hz, 6H), 0.84 (d, 7Hz, 6H); 2.65 (dd, 14Hz, 4Hz, 2H); 2.83 (dd, 14Hz, 10Hz, 2H); 3.34 (m, 2H); 4.43 (dd, 6Hz, 9Hz, 2H); 4.55 (m, 2H); 4.80 (m, 2H); 6.86 (m, 2H); 7.07 (t, 8Hz, 4H); 7.22 (d, 8Hz, 4H); 7.74 (m, 2H); 7.89 (m, 4H); 7.89 (m, 4H); 8.12 (d, 8Hz, 2H); 8.19 (m, 4H); 8.57 (d, 9Hz, 2H); 8.61 (d, 9Hz, 2H).

Example 173

N,N'-bis-(<2-quinolylcarbonyl>-L-asparaginyl)-2S,5S-diamino-1,6-diphenyl-hexane-3R,4R-diol

Synthesis analogous to example 58.

MS (FAB): 861 $(M+Na)^+$

NMR (270 MHz, DMSO <D_6>): 2.33-2.78 (m, 8H); 3.30 (m, 2H); 4.33 (m, 2H); 4.70 (m, 4H); 4.70 (m, 4H); 6.80-8.22 (m, 26H); 8.59 (d, 8Hz, 2H); 8.92 (d, 8Hz, 2H).

Example 174

N,N'-bis-(tert-butoxycarbonyl)-2S,4-diamino-1,5-diphenyl-pentane-3-ol

2.3 g tert.-butoxycarbonyl-L-phenylalanal were dissolved in 10 ml ethanol. After addition (at 0°C) of 0.05 ml tetramethyl guanidine and a solution of 2.42 g 2-nitro-1-phenyl ethane in 2 ml ethanol the solution was

permitted to warm to RT and stand overnight. The solution was concentrated, the remaining light oil (4.8 g) was used again directly.

4.7 g of the oil obtained above were dissolved in 70 ml ethanol. After the addition of 0.1 ml glacial acetic acid an 1 g Raney nickel the solution was shaken for 16 h at 50°C and 25 atm. hydrogen in a glass insert in the autoclave. The catalyst was filtered off; the eluate was evaporated to an oil. The residue was dissolved in water/1N HCl and extracted 4 times with acetic ester. The acetic ester extract was concentrated and used again directly (2.6 g).

2.57 g of the amino compound obtained above were dissolved in 25 ml dioxane at RT. After addition of 0.86 ml triethyl amine and 1.7 g di-tert.-butyldicarbonate the solution was stirred for another 30 min. The solution was concentrated and ice water, acetic ester and $KHSO_4$ were added up to pH 2. The acetic ester phase was washed with aqueous NaCl solution, dried over Na_2SO_4 and concentrated. 3.3 g of an oil were obtained. This was further refined by chromatography on silica gel (CH_2Cl_2/methanol/glacial acetic acid 100/3/0.3). 2.2 g of product were obtained as a mixture of the diastereomers.

MS (FAB): 471 $(M+H)^+$, 371, 315

Example 175

N,N'-bis-(tert.-butoxycarbonyl)-1,3-diaminopropane

MS (FAB): 495 $(M+Na)^+$, 473 $(M+H)^+$

NMR (270 MHz, $CDCl_3$): 0.97 (dd, 12H); 1.45 (s, 18H); 1.70 (T, 6Hz, 2H); 2.03 (m, 2H); 3.08 (m, 2H); 3.58 (m, 2HO; 3.88 (dd, 2H); 5.09 (d, 2H); 7.21 (s, 2H).

Example 176

N,N'-bis-(tert.-butoxycarbonyl)-1,3-diaminopropane-2-ol.

MS (FAB/LiCl): 495 $(M + Li)^+$

NMR (270 MHz, $CDCl_3$): 0.97 (dd, 12H); 1.45 (s, 18H); 20.4 (m, 2H); 3.20 (m, 2H); 3.61 (m, 2H); 3.90 (dd, 2H); 3.95 (m, 1H); 5.16 (dd, 2H); 7.18 (s, 1H); 7.49 (s, 1H).

Example 177

N,N'-bis-(tert.-butoxycarbonyl)-1,3-diaminoacetone

MS (FAB/LiCl): 493 $(M+Li)^+$

NMR (270 MHz, $CDCl_3$): 0.98 (dd, 12H); 1.45 (s. 18H); 2.09 (m, 2H); 3.94 (dd, 2H); 4.10 (s, 2H); 4.18 (s, 2H); 5.20 (d, 2H); 7.50 (s, 2H).

Example 178

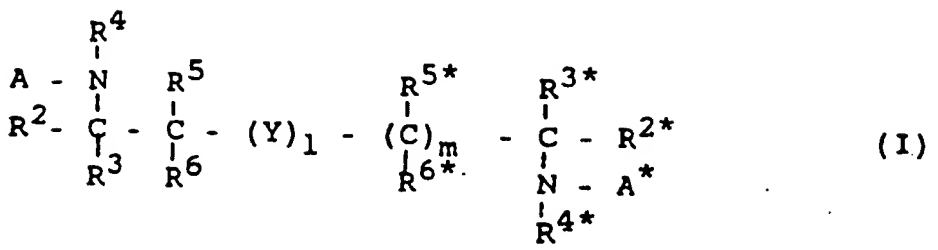
N,N'-bis-(tert.-butoxycarbonyl)-1,4-diaminobutane-2-on

MS (FAB): 523 $(M+Na)^+$, 501 $(M+H)^+$

NMR (270 MHz, $CDCl_3$): 0.95 (m, 12H); 1.43 (d, 18H); 2.09 (m, 2H); 2.69 (m, 2H); 3.45 (m, 1H); 3.86 (m, 1H); 3.90 (m, 1H); 3.99 (m, 1H); 4.18 (m, 1H); 5.23 (d, 2H); 6.91 (s, 1H); 7.17 (s, 1H).

Claims

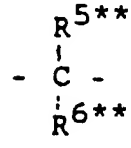
1. Compound of formula I



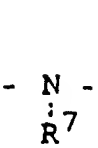
(I)

wherein

Y stands for oxygen, sulfur a radical of formula II or a radical of formula III



(II)



(III)

l and m, independent of each other, are 0 or 1;

A means a radical of formula IV and A* a radical of formula IV*

$$D - (E)_n - (F)_o - (G)_p - \qquad (IV)$$

$$D^* - (E^*)_{n^*} - (F^*)_{o^*} - (G^*)_{p^*} - (IV^*)$$

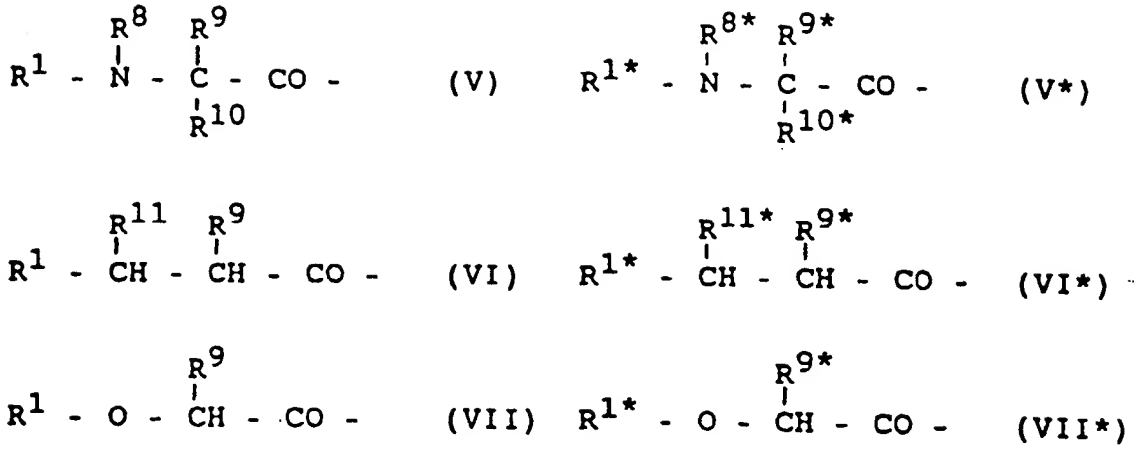
where

E, E*, F, F*, G and G*, independent of one another, stand for a natural or an unnatural amino acid, azaamino acid or imino acid;

n, n*, o, o*, p and p*, independent of one another, mean 0 or 1;

D stands for R^1 or a radical of formulas V, VI or VII, and

D* stands for R^{1*} or a radical of formulas V*, VI* or VII*



and wherein R^1 and R^{1*}, independent of each other, stand for

a_1)

- hydrogen
- carboxyl.
- (C_1-C_{18})-alkyl, which may be simply or doubly unsaturated and which may be substituted by up to 3 identical or different radicals from the series
- mercapto,
- hydroxy,
- (C_1-C_7)-alkoxy,
- carbamoyl
- (C_1-C_8)-alkanoyloxy,
- carboxy,
- (C_1-C_7)-alkoxycarbonyl,
- F, Cl, Br, I,
- amino
- amidino, which if appropriate can be substituted by one, two or three (C_1-C_8)-alkyl radicals,

- guanidino, which if appropriate can be substituted by one or two benzyloxycarbonyl radicals or by one, two, three or four (C_1-C_8)-alkyl radicals,
- (C_1-C_7)- alkylamino,
- di-(C_1 -C_7)-alkylamino,
- (C_1-C_6)-alkoxycarbonylamino,
- (C_7-C_{15})-aralkoxycarbonyl,
- (C_7-C_{15})-aralkoxycarbonylamino,
- Phenyl-(C_1-C_4)-alkoxy,
- 9-fluorenylmethoxycarbonylamino,
- (C_1-C_6)-alkylsulfonyl,
- (C_1-C_6)-alkylsulfinyl,
- (C_1-C_6)-alkylthio,
- hydroxamino,
- hydroximino,
- sulfamoyl,
- sulfo,
- carboxamido,
- formyl,
- hydrazono,
- imino,
- a radical $CONR^{12}R^{13}$ or $CONR^{12*}R^{13*}$,
- by up to six hydroxy or
- by up to five (C_1-C_8)-alkanoxyloxy;
- mono-, bi- or tri-cyclic (C_3-C_{18})-cycloalkyl,

- (C_3-C_{18})-cycloalkyl-(C_1-C_6)-alkyl, the cycloalkyl part in each case being substituted if appropriate by one or two identical or different radicals from the series

- F, Cl, Br, I,
- carboxy,
- carbamoyl,
- carboxymethoxy,
- hydroxy,
- (C_1-C_7)-alkoxy,
- (C_1-C_7)-alkyl,
- (C_1-C_7)-alkyloxycarbonyl,
- amino,
- (C_1-C_6)-alkylamino-(C_1-C_6)-alkyl,
- di-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl,
- amidino,
- hydroxamino,
- hydroximino,
- hydrazono,
- imino,
- guanidino,
- (C_1-C_6)-alkoxysulfonyl,
- (C_1-C_6)-alkoxysulfinyl,
- (C_1-C_6)-alkoxycarbonylamino
- (C_6-C_{12})-aryl-(C_1-C_4)-alkoxycarbonylamino,
- (C_1-C_7)-alkylamino,
- di-(C_1-C_7)-alkylamino and

- trifluoromethyl;
- (C_6-C_{14})-aryl,
- (C_6-C_{14})-aryl-(C_1-C_6)-alkyl,
- (C_6-C_{14})-aryloxy-(C_1-C_6)-alkyl or
- (C_6-C_{14})-aryl-(C_3-C_8)-cycloalkyl, wherein the aryl part in each case is substituted if appropriate by one, two or three identical or different radicals from the series
- F, Cl, Br, I,
- hydroxy,
- mono-, di- or tri-hydroxy-(C_1-C_4)-alkyl,
- trifluoromethyl,
- formyl,
- carboxamido,
- mono- or di-(C_1-C_4)-alkylaminocarbonyl,
- nitro,
- (C_1-C_7)-alkoxy,
- (C_1-C_7)-alkyl,
- (C_1-C_7)-alkoxycarbonyl,
- amino,
- (C_1-C_7)-alkylamino,
- di-(C_1-C_7)-alkylamino,
- carboxy,
- carboxymethoxy,
- amino-(C_1-C_7)-alkyl,
- (C_1-C_7)-alkylamino-(C_1-C_7)-alkyl,
- di-(C_1-C_7)-alkylamino-(C_1-C_7)-alkyl,

- (C_1-C_7)-alkoxycarbonylmethoxy,
- carbamoyl,
- sulfamoyl,
- (C_1-C_7)-alkoxysulfonyl,
- (C_1-C_8)-alkylsulfonyl,
- sulfo-(C_1-C_8)-alkyl
- guanidino (C_1-C_8)-alkyl and
- (C_1-C_6)-alkoxycarbonylamino;
- het,
- het-(C_1-C_6)-alkyl,
- het-(C_3-C_8)-cycloalkyl,
- het-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkyl,
- het-(C_3-C_8)-cycloalkoxy-(C_1-C_4)-alkyl,
- het-thio-(C_1-C_6)-alkyl,
- het-thio-(C_3-C_8)-cycloalkyl,
- het-thio-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkyl,

where in each case het stands for the radical of a 5- to 7-member monocyclic or 8- to 10-member bicyclic ring system which can be benzanellated, aromatic, partly hydrogenated or completely hydrogenated, which can contain as heteroelements one, two, three or four different radicals from the group N, O, S, NO, SO, SO_2, which can be substituted with 1 to 6 hydroxy and which, if appropriate, is mono-, di- or tri-substituted as defined for (C_6-C_{14})-aryl under a_1) and/or with oxo,

or mean a radical $NR^{12}R^{13}$ or $NR^{12*}R^{13*}$,

or

a_2)

- a radical of formula VIII or VIII*

R^{1a}-W (VIII)

R^{1a*}-W* (VIII*)

wherein R^{1a} and R^{1a*} are defined like R^1 and R^{1*} under a_1) and W and W* stand for -CO-, -CS-, O-CO-, -SO_2-, -SO-, -S-, -$NHSO_2$-, -NHCO-, -CH(OH)-, N(OH)- or -CO-V- with V meaning a peptide with 1 to 10 amino acids;

or wherein R^1 and R^{1*}, independent of each other, together with R^{11} or R^{12} and the atoms that carry them form monocyclic or bicyclic, saturated or partly unsaturated ring systems with 5-12 ring members which in addition to carbon can also contain 1 sulfur atom, which may be oxidized to sulfoxide or sulfone;

a_3)

- a glycosyl radical, preferably a glucofuranosyl or glucopyranosyl radical, which is derived from naturally occurring aldotetroses, aldopentoses, aldohexoses, ketopentoses, ketohexoses, desoxyaldoses, aminoaldoses and oligosaccharides as well as their stereoisomers;

R^2 and R^{2*}

are defined independent of each other like R^1 and R^{1*} under a_1) or a_2) or together with R^4 or R^{4*} and the atoms carrying them form mono- or bicyclic, saturated or partly unsaturated ring systems with 5 to 12 ring members, or together with R^3 or R^{3*} and the atoms carrying them form cyclic, saturated or partly unsaturated ring systems with 3 to 12 ring members;

R^3 and R^{3*}

independent of each other mean

- hydrogen or

- (C_1-C_3)-alkyl;

R^4 and R^{4*},

independent of each other, mean

- hydrogen or

- (C_1-C_8)-alkyl;

R^5, R^{5*} and R^{5**},

independent of one another, mean

- hydrogen.

- hydroxy,

- amino or

- carboxy, or

with R^6, R^{6*} or R^{6**} together with the carbon atoms carrying these, in each case independent of one another, form a keto group;

R^6, R^{6*} and R^{6**},

independent of one another, mean

- hydrogen or

- (C_1-C_6)-alkyl or

in the case of l=0, R^6 and R^{6*} can possibly form a common bond;

R^7 means

- hydrogen,

- hydroxy or

- (C_1-C_6)-alkyl;

R^8 and R^{8*},

independent of each other, mean

- hydrogen or

- (C_1-C_8)-alkyl, or together with R^9 or R^{9*} and the atoms carrying these form mono- or bicyclic, saturated or partly unsaturated ring systems with 5 to 12 ring members;

R^9 and R^{9*}

independent of each other are defined like R^1 or R^{1*} under a_1), stand for hydroxy or (C_1-C_4)-alkanoyloxy, or together with R^{10} or R^{10*} and the atoms carrying these form cyclic, saturated or partly unsaturated ring systems with 3 to 12 ring members;

or

together with R^{11} or R^{11*} and the atoms carrying these form a mono- or bicyclic, saturated or partly unsaturated ring system with 5-12 ring members, which in addition to carbon can also contain 1 sulfur atom, which possibly can be oxidized to sulfoxide or sulfone; or can contain 1 nitrogen atom, the ring system possibly being substituted by amino;

R^{10} and R^{10*},

independent of each other, mean

- hydrogen or
- (C_1-C_6)-alkyl;

R^{11} and R^{11*},

independent of each other, mean

- hydrogen,
- hydroxy,
- (C_1-C_4)-alkanoyloxy or
- (C_1-C_8)-alkyl;

R^{12}, R^{12*}, R^{13} and R^{13*},

independent of one another, mean

- hydrogen,
- (C_1-C_8)-alkyl which can be substituted by
- amino,

- (C_1-C_4)-alkylamino,
- di-(C_1-C_4)-alkylamino,
- mercapto,
- carboxy,
- hydroxy or
- (C_1-C_4)-alkoxy,
- (C_3-C_7)-cycloalkyl,
- (C_1-C_4)-alkoxycarbonyl,
- (C_6-C_{14})-aryl, (C_6-C_{14})-aryl-(C_1-C_4)-alkoxycarbonyl which in the aryl part can be substituted as described for R^1 or R^{1*},
- het or
- het-(C_1-C_4)-alkyl, het being defined as described for R^1 or R^{1*},

or where R^{12} and R^{13} or R^{12*} and R^{13*} together with the nitrogen atoms carrying these form monocyclic or bicyclic, saturated, partly unsaturated or aromatic ring systems which in addition to carbon can also contain 1 or 2 nitrogen atoms, 1 sulfur atom or 1 oxygen atom as further ring members and which can be substituted by

(C_1-C_4)-alkyl,

where

in the compounds of formula I cited above, one or more amide groups (-CONH-) of the main chain can be replaced by $-CH_2NR^{14}-$, $-CH_2S-$, $-CH_2O-$, $-OCH_2-$, $-CH_2CH_2-$, -CH=CH-(cis and trans), $-COCH_2-$, $-CH(OH)CH_2-$, $-CH_2SO-$, $-CH_2SO_2-$, -COO-, $-P(O)(OR^{15})CH_2-$ and $-P(O)(OR^{15})NH-$, or also by an amide group with reversed polarity (-NHCO-);

wherein R^{14} and R^{15},

independent of each other, stand for

- hydrogen or

- (C_1-C_4)-alkyl;

as well as their physiologically tolerated salts.

2. Compound of formula I according to claim 1, characterized in that the radicals and symbols with and without asterisk are in each case identical.

3. Compound of formula I according to claims 1 and 2, characterized in that the compound is C_2-symmetrical.

4. Compound of formula I according to claims 1-3, characterized in that

Y stands for a radical of formula II or a radical of formula II;

l, m, A, A*, D, D*, n, n*, o, o*, p and p* are defined as in claim 1;

E, E*, F, F*, G and G*, independent of each other, stand for a natural or unnatural α-amino acid or α-imino acid;

R^1 and R^{1*},

independent of each other, stand for

a_1) - hydrogen,

- carboxyl,

- (C_1-C_{16})-alkyl, which may be simply saturated and which may be substituted by up to 2 identical or different radicals from the series

- hydroxy,

- (C_1-C_4)-alkoxy,

- carbamoyl,

- (C_1-C_8)-alkanoyloxy,

- carboxy,

- (C_1-C_4)-alkoxycarbonyl,

- F,

- amino,
- (C_1-C_7)-alkylamino,
- di-(C_1-C_7)-alkylamino,
- (C_1-C_6)-alkoxycarbonylamino,
- benzyloxycarbonyl,
- benzyloxycarbonylamino,
- 9-fluorenylmethoxycarbonylamino,
- (C_1-C_4)-alkylsulfonyl,
- a radical $CONR^{12}R^{13}$ or $CONR^{12*}R^{13*}$,
- by up to six hydroxy or
- by up to four (C_1-C_8)-alkanoyloxy;
- mono- or bicyclic (C_3-C_{12})-cycloalkyl,
- (C_3-C_{12})-cycloalkyl-(C_1-C_6)-alkyl where in each case the cycloalkyl part is substituted by one or two identical or different radicals from the series
- F,
- carboxy,
- hydroxy,
- (C_1-C_7)-alkoxy,
- (C_1-C_4)-alkyl,
- (C_1-C_4)-alkyloxycarbonyl,
- amino,
- (C_1-C_6)-alkoxycarbonylamino,
- benzyloxycarbonylamino,
- (C_1-C_4)-alkylamino and
- di-(C_1-C_4)-alkylamino;
- (C_6-C_{10})-aryl,

- $(C_6$-$C_{10})$-aryloxy-$(C_1$-$C_6)$-alkyl or

- $(C_6$-$C_{10})$-aryl-$(C_1$-$C_6)$-alkyl, wherein the alkyl part in each case is possibly substituted by one, two or three identical or different radicals from the series

- F, Cl, Br,

- hydroxy,

- hydroxy-$(C_1$-$C_4)$-alkyl,

- carboxamido,

- mono- or di-$(C_1$-$C_4)$-alkylaminocarbonyl,

- $(C_1$-$C_4)$-alkoxy,

- $(C_1$-$C_4)$-alkyl,

- $(C_1$-$C_4)$-alkoxycarbonyl,

- amino,

- $(C_1$-$C_4)$-alkylamino,

- di-$(C_1$-$C_4)$-alkylamino,

- carboxy,

- carbamoyl,

- $(C_1$-$C_4)$-alkoxycarbonylamino;

- het,

- het-$(C_1$-$C_6)$-alkyl,

- het-$(C_5$-$C_6)$-cycloalkyl,

- het-thio-$(C_1$-$C_4)$-alkyl,

- het-thio-$(C_5$-$C_6)$-cycloalkyl,

where het in each case stands for a 5- to 6-member monocyclic or 8- to 10-member bicyclic ring system which can be aromatic, partly hydrogenated or completely hydrogenated, which can contain as heteroelements one, two, three

of four different radicals from the group N, O, S, NO, SO, SO_2, which can be substituted with 1 to 4 hydroxy and which can possibly be mono- or di-substituted as defined for (C_6-C_{10})-aryl under a_1) and/or with oxo,

or means a radical $NR^{12}R^{13}$ or $NR^{12*}R^{13*}$ or,

a_2) - a radical of formula VIII or VIII*

R^{1a} - W (VIII)

R^{1a*} - W* (VIII*)

wherein R^{1a} and R^{1a*} are defined like R^1 an R^{1*} under a_1) and W or W* stand for -CO-, -O-CO-, $-SO_2-$, -SO-, -S-, -NHCO- OR -CH(OH)-;

or wherein R^1 and R^{1*} independent of each other together with R^{11} or R^{11*} and the atoms carrying these form monocyclic, saturated or partly unsaturated ring systems with 5-8 ring members, which in addition to carbon also can contain 1 sulfur atom, which can possibly be oxidized to sulfoxide or sulfone;

a_3) - a glycosyl radical that is defined as in claim 1;

R^2 and R^{2*},

independent of each other, mean

b_1) hydrogen,

- carboxy,

- (C_1-C_{10})-alkyl which is possibly simply or doubly unsaturated and which is possibly substituted by up to 3 identical or different radicals from the series

-hydroxy,

- (C_1-C_7)-alkoxy,

- (C_1-C_7)-alkylthio,

- (C_1-C_7)-alkylsulfinyl,

- (C_1-C_7)-alkylsulfonyl,

- (C_1-C_7)-alkanoyloxy,
- carboxy,
- (C_1-C_7)-alkoxycarbonyl,
- Cl, Br,
- amino,
- amidino,
- guanidino,
- N,N'-di-(benzyloxycarbonyl)-guanidino,
- Carbamoyl,
- (C_7-C_{15})-aralkoxycarbonyl,
- (C_1-C_5)-alkoxycarbonylamino,
- (C_7-C_{15})-aralkoxycarbonylamino or
- 9-fluorenylmethoxycarbonylamino;
- (C_3-C_{12})-cycloalkyl,
- (C_3-C_{12})-cycloalkyl-(C_1-C_3)-alkyl,
- (C_6-C_{14})-aryl,
- (C_6-C_{14})-aryl-(C_1-C_3)-alkyl, the aryl part in each case possibly being substituted by one, two or three identical or different radicals from the series
- F, Cl, Br, I,
- hydroxy,
- (C_1-C_7)-alkoxy,
- (C_1-C_7)-alkyl,
- (C_1-C_7)-alkoxycarbonyl,
- amino and
- trifluoromethyl; or

- het-(C_1-C_6)-alkyl, het standing for the radical of a 5- or 6-member monocyclic or 9- to 10-member bicyclic, possibly partly or completely hydrogenated heteroaromatic compound with at least 1 C atom, 1-4 N atoms and/or 1-2 S atoms and/or 1-2 O atoms as ring members, which is possibly mono- or di-substituted as described in claim 1 for the aryl part; or

b_2) together with R^4 or R^{4*} and the atoms carrying these form pyrrolidine or piperidine, which in each case can also be annelated, with cyclopentyl, cyclohexyl or phenyl,

or together with R^3 or R^{3*} and the atoms carrying these form cyclic, saturated or partly unsaturated ring systems with 3-8 ring members;

R^3 and R^{3*}

independent of each other mean

- hydrogen,
- methyl or
- ethyl;

R^4 and R^{4*}

independent of each other mean

- hydrogen,
- (C_1-C_4)-alkyl;

R^5, R^{5*} and R^{5**}

independent of each other are as defined in claim 1;

R^6, R^{6*} and R^{6**}

independent of one another mean

- hydrogen,
- (C_1-C_4)-alkyl;

R^7

means

- hydrogen,

- hydroxy or

- C_1-C_4)-alkyl;

R^8 and R^{8*}

independent of each other mean

- hydrogen,

- (C_1-C_8)-alkyl or together with R^9 or R^{9*} and the atoms carrying these form pyrrolidine or piperidine, which in each case can additionally be annelated with cyclopentyl, cyclohexyl or phenyl;

R^9 and R^{9*}

independent of each other are defined like R^2 or R^{2*} under b_1), or mean (C_1-C_8)-alkyl, or

together with R^{10} or R^{10*} and the atoms carrying these form a mono- or bicyclic, saturated or partly unsaturated ring system with 5-12 ring members;

or

together with R^{11} or R^{11*} and the atoms carrying these form a mono- or bicyclic, saturated or partly unsaturated ring system with 5-12 ring elements, which in addition to carbon can also contain 1 sulfur atom which can possibly be oxidized to sulfoxide or sulfone;

R^{10} and R^{10*}

independent of each other mean

- hydrogen or

- (C_1-C_4)-alkyl;

R^{11} and R^{11*}

independent of each other mean

- hydrogen,

- hydroxy,

- (C_1-C_4)-alkanoyloxy or

- (C_1-C_4)-alkyl;

R^{12}, R^{12*}, R^{13} and R^{13*}

independent of one another mean

- hydrogen,

- (C_1-C_8)-alkyl, which can be substituted by

- amino,

- (C_1-C_4)-alkylamino,

- di-(C_1-C_4)-alkylamino,

- carboxy,

- hydroxy or

- (C_1-C_4)-alkoxy,

- (C_1-C_{14})-alkoxycarbonyl,

- (C_6-C_{10})-aryl, which can be substituted as described for R^1 or R^{1*},

- (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonyl,

- het or

- het-(C_1-C_4)-alkyl, het being defined as described for R^1 or R^{1*},

it being possible in the aforementioned compounds of formula I for one or more amide groups (-CONH-) of the main chain to be replaced by a group consisting of $-CH_2-NR^{14}-$, $-CH_2-O-$, $-CH_2CH_2-$, $-COCH_2-$, $-CH(OH)CH_2-$, -COO- or by an amide group of reverse polarity (-NHCO-);

R^{14} stands for

- hydrogen or

- (C_1-C_4)-alkyl;

as well as their physiologically tolerated salts.

5. Compounds of formula I as described in claims 1 to 4, characterized in that

Y stands for a radical of formula II or a radical of formula III;

l, m, A, A*, D, D*, n, n*, o, o* are defined as in claim 1,

p and p* stand for 1;

R^1 and R^{1*}

independent of each other stand for

- hydrogen,
- carboxyl,
- (C_1-C_{10})-alkyl,
- (C_3-C_8)-cycloalkyl,
- (C_3-C_8)-cycloalkyl-(C_1-C_{10})-alkyl,
- phenyl-(C_1-C_8)-alkyl, which in the phenyl part can be substituted as in claim 4,
- possibly protected mono- or di-amino-(C_1-C_{12})-alkyl or amino-(C_6-C_{10})-aryl-(C_1-C_4)- alkyl or amino-(C_3-C_{10})-cycloalkyl-(C_1-C_4)-alkyl, such as -2-amino-3-phenyl-propyl,
- mono-, di-, tris-, tetra-, penta- or hexahydroxy-(C_1-C_{10})-alkyl or -alkanoyl,
- (C_1-C_4)-alkoxy-(C_1-C_{10})-alkyl,
- (C_1-C_4)-alkoxycarbonyl-(C_1-C_{10})-alkyl,
- (C_1-C_{16})-alkylsulfonyl,
- (C_1-C_8)-alkylsulfinyl,
- mono-, di-, trihydroxy-(C_1-C_8)-alkylsulfonyl,
- mono-, di-, trihydroxy-(C_1-C_8)-alkylsulfinyl,
- mono-, di-, tri- or tetra-(C_1-C_8)-alkanoyloxy-(C_1-C_{10})-alkyl,

- (C_1-C_{14})-alkanoyl,
- possibly protected amino-(C_1-C_{11})-alkanoyl,
- di-(C_1-C_7)-alkylamino-(C_2-C_{11})-alkanoyl,
- (C_1-C_9)-cycloalkylcarbonyl,
- amino-substituted (C_3-C_9)-cycloalkylcarbonyl,
- amino-substituted (C_3-C_9)-cycloalkylsulfonyl,
- (C_6-C_{10})-aryl-(C_2-C_{11})-alkanoyl,
- (C_6-C_{10})-aryloxy-(C_2-C_{11})-alkanoyl,
- benzoyl, benzenesulfonyl or (C_6-C_{10})-aryl-(C_1-C_4)-alkylcarbonyl or -sulfonyl possibly substituted by amino, halogen, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxy or (C_1-C_7)-alkoxycarbonyl,
- (C_1-C_{10})-alkoxycarbonyl,
- substituted (C_1-C_{10})-alkoxycarbonyl
- (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl,
- (C_6-C_{10})-aryl-(C_1-C_8)-alkyl, (C_3-C_{10})-cycloalkyl-(C_1-C_8)-alkyl or (C_1-C_{10}) substituted by possibly protected amino and hydroxy,
- 9-flourenylmethoxycarbonyl,
- ketohexosyl,
- ketopentosyl,
- deoxyhexoketosyl,
- dexoypentoketosyl,
- aldohexosyl,
- aldopentosyl,
- deoxyhexoaldosyl,
- deoxypentoaldosyl,
- 2-amino-2-deoxyhexosyl

- 2-acetamido-2-dexoyhexosyl,

- lactosyl or

- maltosyl, it being possible for the joined sugar to be present in the pyranose or furanose form,

- het-(C_1-C_6)-alkyl,

- het-carbonyl or -sulfonyl,

- het-(C_1-C_6)-alkylcarbonyl or -sulfonyl,

- het-mercapto-(C_1-C_6)-alkylcarbonyl or -sulfonyl,

het in each case standing for

furyl, thienyl, benzothienyl, benzodioxolanyl, pyrrolyl, imidazolyl, isoxazolyl, thiazolyl, pyrazolyl, triazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolidyl, piperidyl, piperazinyl, morpholino, thiomorpholino, tetrahydrofuryl, tetrahydropyryl, tetrahydrothienyl, indolyl, quinolyl or isoquinolyl,

it also being possible for these to be substituted by one or two identical or different radicals from the group (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkoxycarbonylamino, hydroxy, amino, mono- or di-(C_1-C_4)-alkylamino and oxido;

R^2 and R^{2*}

independent of each other mean

- hydrogen,

- carboxyl,

- (C_1-C_8)-alkyl, which is possibly substituted by up to 2 identical or different radicals from the series

- hydroxy,

- (C_1-C_4)-alkoxy,

- (C_1-C_4)-alkylthio,
- (C_1-C_4)-alkylsulfinyl,
- (C_1-C_4)-alkylsulfonyl,
- (C_1-C_4)-alkanoyloxy,
- carboxy,
- (C_1-C_4)-alkoxycarbonyl,
- amino,
- amidino,
- guanidino,
- N,N'-di-(benzyloxycarbonyl)-guanidino,
- carbamoyl,
- (C_6-C_{10})-aryl-(C_1-C_3)-alkoxycarbonyl,
- (C_1-C_5)-alkoxycarbonylamino,
- (C_6-C_{10})-aryl-(C_1-C_3)-alkoxycarbonylamino, or
- (C_3-C_{10})-cycloalkyl,
- (C_3-C_{10})-cylcoalkyl-(C_1-C_3)-alkyl,
- (C_1-C_4)-alkyl-(C_3-C_{10})-cycloalkyl-(C_1-C_3)-alkyl,
- (C_6-C_{10})-aryl,
- (C_6-C_{10})-aryl-(C_1-C_3)-alkyl, the aryl part possibly being substituted by one, two or three identical or different radicals from the series
- F, Cl, Br,
-hydroxy,
- (C_1-C_4)-alkoxy,
- (C_1-C_4)-alkyl,
- (C_1-C_4)-alkoxycarbonyl and
- amino, or

- het-(C_1-C_4)-alkyl, het being defined as for R^1 or R^{1*},

R^3 and R^{3*}

independent of each other mean

- hydrogen or

- methyl,

R^4 and R^{4*}

independent of each other mean

- hydrogen or

- methyl,

R^5, R^{5*} and R^{5**}

independent of one another mean

- hydrogen,

- hydroxy,

- amino or

- carboxy;

R^6, R^{6*} and R^{6**}

independent of one another mean

- hydrogen or

- methyl;

R^7 means

- hydrogen,

- hydroxy or

- methyl;

R^8 and R^{8*}

independent of each other mean

- hydrogen,

- methyl, ethyl or n-propyl, or together with R^9 or R^{9*} and the atoms carrying these form a 1,2,3,4-tetrahydroisoquinoline or a 2-azabicyclooctane skeleton;

R^9 and R^{9*}

independent of each other are defined like R^2 and R^{2*} in claim 4, or mean (C_1-C_8)-alkanoyloxy or

together with R^{10} or R^{10*} and the atoms carrying these form cyclic ring systems with 5 to 7 ring members;

or together with R^{11} or R^{11*} form a form a thiochroman system the sulfur atom of which can if appropriate be oxidized to sulfone;

R^{10} and R^{10*}

independent of each other mean

- hydrogen or
- methyl;

R^{11} and R^{11*} are defined as in claim 4;

in the aforementioned compounds of formula I one or more amide groups (-CONH-) of the main chain can be replaced as defined in claim 4;

R^{14} stands for

- hydrogen or
- methyl;

as well as their physiologically tolerated salts.

6. Compound of formula I as contained in claims 1 to 5, characterized in that

R^1 and R^{1*}

independent of each other stand for

a_1) - hydrogen,

- carboxyl,

- (C_1-C_{16})-alkylsulfonyl

- (C_1-C_8)-alkylsulfinyl,

- (C_1-C_8)-mono-, di- or tri-hydroxyalkylsulfonyl,

- hydroxy-(C_1-C_{10})-alkanoyl,

- mono-, di-, tri- or tetra-hydroxy-(C_1-C_4)-alkyl,

- (C_1-C_8)-alkanoyloxy-(C_1-C_{10}) alkyl,

- 1,2-diacetoxyethyl,

- 1,2,3-triacetoxypropyl,

- (C_1-C_{14})-alkanoyl,

- amino-(C_1-C_{12})-alkanoyl,

- N-(C_1-C_4)-alkoxycarbonylamino-(C_1-C_8)-alkyl,

- di-(C_1-C_7)-alkylamino-(C_2-C_{11})-alkanoyl,

- (C_3-C_9)-cycloalkylcarbonyl,

- amino-(C_3-C_8)-cycloalkylcarbonyl,

- amino-(C_3-C_8)-cycloalkylsulfonyl,

- phenyl,

- (C_6-C_{10})-aryl-(C_2-C_{11})-alkanoyl,

- (C_6-C_{10})-aryloxy-(C_2-C_{11})-alkanoyl,

- benzoyl or benzenesylfonyl, possibly substituted by halogen, amino, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxy or (C_1-C_7)-alkoxycarbonyl,

- benzylsulfonyl, benzylsulfinyl or benzylthio, possibly substituted by halogen, amino, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxy or (C_1-C_7)-alkoxycarbonyl,
- 4-chlorobenzylsulfonyl,
- amino,
- (C_1-C_4)-alkoxycarbonylamino,
- (C_1-C_{12})-alkanoyl which is substituted by hydroxy, amino and possibly by phenyl or cyclohexyl,
- possibly protected, amino-substituted (C_6-C_{10})-aryl- or (C_3-C_{10})-cycloalkyl-(C_1-C_4)-alkyl or (C_1-C_8)-alkyl,
- (C_1-C_{10})-alkoxycarbonyl,
- substituted (C_1-C_{10})-alkoxycarbonyl,
- (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl,
- 9-fluorenylmethoxycarbonyl,
- 1-deoxyhexoketosyl or 1-deoxypentoketosyl,
- hexosyl or pentosyl
- 6-deoxyhexosyl,
- amino sugar radicals,
- lactosyl,
- maltosyl,

it being possible for the joined sugar to be present in the pyranose or furanose form,

- het,
- het-carbonyl or het-sulfonyl,
- het-(C_1-C_6)-alkyl,
- het-(C_1-C_6)-alkanoyl
- het-(C_1-C_6)-alkylsulfonyl or

- het-mercapto-(C_1-C_3)-alkylcarbonyl,

het standing in each case for

- pyrrolyl,
- imidazolyl,
- pyridyl,
- pyrimidyl,
- pyrrolidyl,
- piperidyl,
- morpholino,
- quinolyl or
- isoquinolyl,

and also possibly being substituted by one or two identical or different radicals from the group (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkoxycarbonylamino, hydroxy, amino, mono- or di-(C_1-C_4)-alkylamino;

R^2 and R^{2*}

independent of each other stand for

- hydrogen,
- carboxyl,
- methyl, ethyl, isopropyl, n-propyl, n-butyl, isobutyl, sec.-butyl, n-pentyl, n-hexyl,
- cyclohexyl,
- cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl,
- 4-methylcyclohexylmethyl,
- 1-decahydronaphthylmethyl, 2-decahydronaphthylmethyl,
- phenyl,
- benzyl,

- 2-phenylethyl,
- 1-naphthylmethyl, 2-naphthylmethyl,
- 2-methylbenzyl, 3- methylbenzyl, 4-methylbenzyl,
- 2,4,6-trimethylbenzyl,
- 4-tert.-butylbenzyl,
- 4-tert.-butoxybenzyl
- 4-hydroxybenzyl,
- 4-methoxybenzyl,
- 2,4-dimethoxybenzyl,
- 3,4-dihydroxybenzyl,
- 3,4-dimethoxybenzyl,
- (benzodioxolane-5-yl)methyl,
- 4-chlorobenzyl,
- hydroxymethyl,
- 1-hydroxyethyl,
- 4-pyridyl,- 4-(N-oxidopyridyl),
- 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-(4-pyridyl)-ethyl,
- 2-thienylmethyl, 3- thienylmethyl,
- 2-(2-thienyl)ethyl, 2-(3-thienyl)ethyl,
- indole-2-yl-methyl, indole-3-yl-methyl,
- (1-methyl-imidazole-4-yl)methyl,
- imidazole-4-yl-methyl, imidazole-1-yl-methyl,
- 2-thiazolylmethyl,
- 3-pyrazolylmethyl,
- 4-pyrimidylmethyl,
- 2-benzo[b]thienylmethyl, 3-benzo[b]thienylmethyl,

- 2-furylmethyl,

- 2-(methylthio)ethyl,

- 2-(methylsulfinyl)ethyl

R^3, R^{3*}, R^4, R^{4*}, R^6, R^{6*}. R^{10} and R^{10*}

mean hydrogen;

R^5 and R^{5*}

independent of each other stand for

- hydrogen,

- hydroxy or

- amino;

R^7 means

- hydroxy or

- methyl;

R^8 and R^{8*}

independent of each other mean

- hydrogen or

together with R^9 or R^{9*} and the atoms carrying these form a 1,2,3,4-tetrahydroisoquinoline or 2-azabicyclooctane skeleton;

R^9 and R^{9*}

independent of each other are defined like R^2 or R^{2*} or mean

- hydroxy,

- acetoxy,

- tert.-butoxymethyl,

- 3-guanidinopropyl,

- carbamoylmethyl, carbamoylethyl,

- carboxymethyl, carboxyethyl,

- mercaptomethyl,

- (1-mercapto-1-methyl)ethyl,

- aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl,

- N,N-dimethylamino,

- N,N'-di-(benzyloxycarbonyl)-guanidino-propyl,

- 2-benzyloxycarbonylethyl, benzyloxycarbonylmethyl,

- tert.-butylsulfonylmethyl

- 4-benzylcarbonylaminobutyl;

R^{11} and R^{11*}

independent of each other mean

- hydrogen,

- hydroxy or

- acetoxy,

and in the aforementioned compounds of this invention one or more amide groups (-CONH-) of the main chain can be replaced by $-CH_2NR^{14}-$ or $-CH(OH)CH_2-$;

R^{14} stands for

- hydrogen or

- methyl;

as well as their physiologically tolerated salts.

7. Compound of formula I as contained in claims 1 to 6, characterized in that

R^1 and R^{1*}

independent of each other stand for

$-a_1$) - hydrogen,

- carboxyl,

- (C_1-C_{16})-alkylsulfonyl,

- (C_1-C_8)-mono- or -dihydroxyalkylsulfonyl,
- mono-, di- or trihydroxy-(C_1-C_3)-alkyl,
- (C_1-C_8)-alkoxycarbonyl,
- (C_1-C_{14})-alkanoyl,
- amino-(C_1-C_{12})-alkanoyl,
- (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonyl,
- (C_6-C_{10})-aryl-(C_1-C_4)-alkylcarbonyl,
- 9-fluorenylmethoxycarbonyl,
- (C_1-C_4)-alkanoyloxy-(C_1-C_6)-alkyl,
- 1,2-diacetoxyethyl,
- 1,2,3-triacetoxypropyl,
- phenyl
- benzolsulfonyl possibly substituted by halogen, amino, (C_1-C_4)-alkyl or methoxy,
- benzolsulfonyl, -sulfinyl or - thio possibly substituted by halogen, amino, (C_1-C_4)-alkyl or methoxy,
- het or het-sulfonyl,
- het-(C_1-C_4)-alkanoyl,
- het-mercapto-(C_1-C_3)-alkylcarbonyl,

het in each case standing for

- pyrrolyl,
- imidazolyl,
- pyridyl,
- pyrimidyl,
- pyrrolidyl,
- quinolyl,

- isoquinolyl,

- piperidyl or

- morpholino,

it also being possible that this radical is substituted by one or two identical or different radicals from the group methyl, amino and (C_1-C_4)-alkoxycarbonylamino,

- amino-(C_3-C_6)-cycloalkylcarbonyl,

- (C_1-C_8)-alkanoyl, which is substituted by hydroxy and amino and possibly by phenyl or cyclohexyl,

- possibly protected amino-substituted phenyl- or cyclohexyl-(C_1-C_6)-alkyl,

- amino,

- (C_1-C_4)-alkoxycarbonylamino,

- benzyloxycarbonylamino,

- 1-deoxyhexoketosyl or 1-deoxypentoketosyl,

- hexosyl or pentosyl, it being possible for the joined sugar to be present in the pyranose or the furanose form,

R^2 and R^{2*}

independent of each other stand for

- hydrogen,

- methyl, ethyl, isopropyl, n-propyl, n-butyl, isobutyl, sec.-butyl, pentyl, hexyl,

- cyclopentylmethyl, cyclohexylmethyl,

- 4-methylcyclohexylmethyl,

- benzyl,

- 2-phenylethyl,

- 1-naphthylmethyl, 2-naphthylmethyl,

- 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl,
- 2,4,6-trimethylbenzyl,
- 4-tert.-butylbenzyl,
- 4-methoxybenzyl,
- 3,4-dihydroxybenzyl,
- 2,4-dimethoxybenzyl,
- 3,4-dimethoxybenzyl,
- 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl or
- 3,4-dimethylenedioxylbenzyl,
- 2-(4-pyridyl)ethyl;

R^3, R^{3*}, R^4, R^{4*}, R^6, R^{6*}, R^7, R^{10} AND R^{10*}

mean hydrogen;

R^5 and R^{5*}

independent of each other mean

- hydrogen or
- hydroxy;

R^8 and r^{8*} independent of each other are defined as in claim 6,

R^9 and R^{9*}

independent of each other are defined like R^9 an R^{9*} in claim 6;

R^{11} and R^{11*} independent of each other are defined as in claim 6,

as well as their physiologically tolerated salts.

8. Compound of formula I as contained in claims 1 to 7, characterized in that

Y stands for a radical of formula III;

l means 0 or 1;

m means 1;

A, A*, D and D* are defined as in claim 1;

n, n*, o, o*, p and p* independent of one another mean 1;

E, E*, F, F*, G and G* independent of one another stand for an amino acid from the series Val, Lys, Lys(Z), Phe, Chg, Ser, Asn, Gly, Ile, Tbg, Nva or Npg;

R^1 and R^{1*} independent of each other mean

- hydrogen,
- carboxyl,
- methylsulfonyl,
- tert.-butylsulfonyl,
- tert.-butoxycarbonyl,
- 2-hydroxyethylsulfonyl,
- 1,2,3-trihydroxypropyl,
- 1,2,3-triacetoxypropyl,
- benzyloxycarbonyl,
- 4-methylphenylsulfonyl,
- 4-chlorobenzylthio,
- benzylsulfinyl,
- 4-chlorobenzylsulfonyl,
- hexadecylsulfonyl,
- 4-amino-1-piperidyl-sulfonyl,
- N-tert.-butoxycarbonyl-4-amino-1-piperidyl-sulfonyl,
- 4-amino-1-piperidyl-carbonyl,
- N-tert.-butoxycarbonyl-4-amino-1-piperidyl-carbonyl,
- 2-amino-3-phenyl-propyl,
- N-tert.-butoxycarbonyl-2-amino-3-phenyl-propyl,
- 2-amino-1-hydroxy-4-methyl-pentyl,

- deoxyfructos-1-yl,
- mannofuranosyl,
- 4-aminocyclohexylcarbonyl,
- 2-quinolylcarbonyl,
- 4-pyridylthio-acetyl,
- 2-quinolyl carbonyl,
- 1-naphthylacetyl,
- 1-naphthyloxyacetyl,
- 1-(4-pyridyl)-ethylsulfonyl,
- 12-aminododecanoyl,
- 4-(N-oxidopyridyl),
- 4-pyridyl,
- tetradecanoyl,
- phenyl,
- amino or
- tert.-butoxycarbonylamino;

R^2 and R^{2*} independent of each other mean

- hydrogen,
- 2-(4-pyridyl)ethyl,
- isopropyl,
- isobutyl,
- n-pentyl,
- benzyl,
- 3,4-methylenedioxybenzyl,
- 2,4-dimethoxybenzyl,
- 4-tert.-butylbenzyl,

- 2-phenylethyl or

- cyclohexylmethyl;

R^3, R^{3*}, R^4. R^{4*}, R^6, R^{6*}, R^7, R^{10} and R^{10*} mean

- hydrogen;

R^5 and R^{5*} independent of each other mean

- hydrogen or

- hydroxy;

R^8 and R^{8*} mean

- hydrogen, or together with R^9 or R^{9*} and the atoms carrying these form a 1,2,3,4-tetrahydroquinoline-3,4-diyl system;

R^9 and R^{9*} independent of each other mean

- hydrogen,

- hydroxy,

- acetoxy,

- n-propyl,

- isopropyl,

- isobutyl,

- aminomethyl,

- 4-aminobutyl,

- hydroxymethyl,

- tert.-butoxymethyl,

- aminocarbonylmethyl,

- 2-benzyloxycarbonyl-ethyl,

- 4-benzylcarbonylamino-butyl,

- N,N*-di(benzyloxycarbonyl)-guanidino-propyl,

- cyclohexyl,

- cyclohexylmethyl,
- benzyl,
- 2-phenyl-ethyl,
- 4-hydroxy-benzyl,
- 4-methoxy-benzyl,
- 4-tert.-butoxy-benzyl,
- 1-naphthylmethyl,
- 2-thienylmethyl,
- 1-imidazolyl-methyl,
- 3-indolyl-methyl,
- 4-pyridylmethyl,
- 4-(N-oxidopyridyl)methyl,
- 2-methylthio-ethyl,
- 2-methylsulfonyl-ethyl,
- tert.-butylsulfonyl-methyl or
- 2-carboxyl-ethyl;

R^{11} and R^{11*} independent of each other mean

- hydrogen
- hydroxy or
- acetoxy;

it being possible in the aforementioned compounds that one or more amide groups (-CONH-) of the main chain are replaced by $-CH_2NH-$ or $-CH(OH)CH_2-$; as well as their physiologically tolerated salts.

9. Compound of formula I as contained in claims 1 to 8, characterized in that

l = 0;

m = 1;

n + o + p = 1;

D and D* stand for a radical of formula VI or VI*;

R^1 and R^{1*} mean

- (C_1-C_{12})-alkylsulfonyl, which can possibly be substituted by up to 3 identical or different radicals from the series
- hydroxy,
- amino or
- carboxy;

R^2 and R^{2*} independent of each other mean

- hydrogen,
- carboxyl,
- methyl, ethyl, isopropyl, n-propyl, n-butyl, isobutyl, sec.-butyl, pentyl, hexyl,
- cyclohexyl,
- cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl,
- 4-methylcyclohexylmethyl,
- 1-decahydronaphthylmethyl, 2-decahydroanaphthylmethyl,
- phenyl,
- benzyl,
- 2-phenylethyl,
- 1-naphthylmethyl, 2-naphthylmethyl,
- 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl,
- 2,4,6-trimethylenzyl,
- 4-tert.-butylbenzyl,
- 4-tert.-butoxybenzyl,

- 4-hydroxybenzyl,
- 4-methoxybenzyl,
- 2,4-dimethoxybenzyl,
- 3,4-dihydroxybenzyl,
- 3,4-dimethoxybenzyl,
- (benzodioxolane-4-yl)methyl,
- 4-chlorobenzyl,
- hydroxymethyl,
- 1-hydroxyethyl,
- 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-(4-pyridyl)-ethyl,
- 2-thienylmethyl, 3-thienylmethyl,
- 2-(2-thienyl)ethyl, 2-(3-thienyl)ethyl,
- indole-2-yl-methyl, indole-3-yl-methyl,
- (1-methyl-imidazole-4-yl)methyl,
- imidazol-4-yl-methyl, imidazol-1-yl-methyl,
- 2-thiazolylmethyl,
- 3-pyrazolylmethyl,
- 4-pyrimidylmethyl,
- 2-benzo[b]thienylmethyl, 3-benzo[b]thienlymethyl,
- 2-furylmethyl,
- 2-(methylthio)ethyl,
- 2-(methylsulfinyl)ethyl or
- 2-(methylsulfonyl)ethyl;

R^3, R^{3*}, R^4, R^{4*}, R^6, R^{6*}, R^{11} an R^{11*} mean

- hydrogen;

R^5 and R^{5*} mean

- hydroxy;

R^9 and R^{9*}

are defined as in claim 8;

as well as their physiologically tolerated salts.

10. Process for the production of a compound of formula I as contained in claims 1 to 9, characterized in that a fragment with terminal carboxyl group or its reactive derivative is coupled to a corresponding fragment with free amino group, possibly for the protection of other functional groups (a) temporarily introduced protective group(s) is split off, and the compound thus obtained is, if appropriate, converted into its physiologically tolerated salt.

11. Use of a compound of formula I as contained in claims 1 to 9 as a drug.

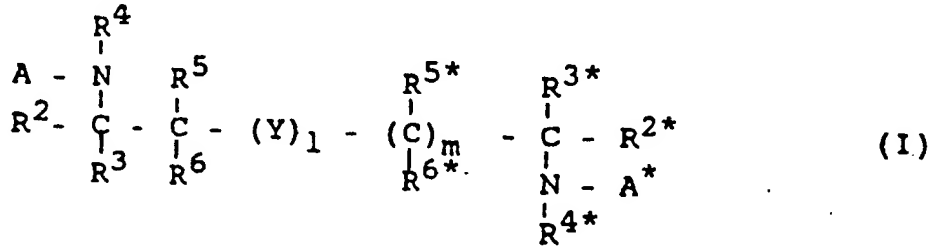
12. Use of a compound of formula I as contained in claims 1 to 9 for inhibiting retroviral proteases.

13. Use of a compound of formula I as contained in claims 1 to 9 in the treatment of "acquired immune deficiency syndrome."

14. Pharmaceutical agent containing a compound of formula I as contained in claims 1 to 9 as well as one or more carriers, if appropriate.

Patent claims for the following treaty countries: ES, GR

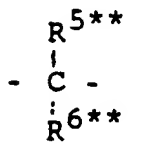
1. Process for the production of a compound of formula I



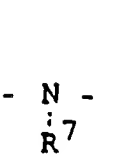
(I)

wherein

Y stands for oxygen, sulfur, a radical of formula II or a radical of formula III



(II)



(III)

l and m, independent of each other, are 0 or 1;

A means a radical of formula IV and A* a radical of formula IV*

$$D - (E)_n - (F)_o - (G)_p - \quad (IV)$$

$$D^* - (E^*)_{n^*} - (F^*)_{o^*} - (G^*)_{p^*} - (IV^*)$$

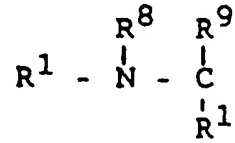
where

E, E*, F, F*, G and G*, independent of one another, stand for a natural or an unnatural amino acid, azaamino acid or imino acid;

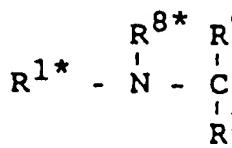
n, n*, o, o*, p and p*, independent of one another, mean 0 or 1;

D stands for R^1 or a radical of formulas V, VI or VII, and

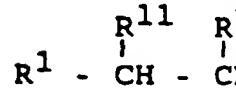
D* stands for R^{1*} or a radical of formulas V*, VI* or VII*



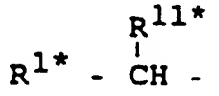
(V)



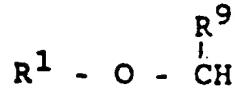
(V*)



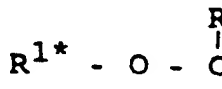
(VI)



(VI*)



(VII)



(VII*)

and wherein R^1 and R^{1*}, independent of each other, stand for

a_1)

- hydrogen

- carboxyl.

- (C_1-C_{18})-alkyl, which may be simply or doubly unsaturated and which may be substituted by up to 3 identical or different radicals from the series

- mercapto,

- hydroxy,

- (C_1-C_7)-alkoxy,

- carbamoyl

- (C_1-C_8)-alkanoyloxy,

- carboxy,

- (C_1-C_7)-alkoxycarbonyl,

- F, Cl, Br, I,

- amino

- amidino, which if appropriate can be substituted by one, two or three (C_1-C_8)-alkyl radicals,

- guanidino, which if appropriate can be substituted by one or two benzyloxycarbonyl radicals or by one, two, three or four (C_1-C_8)-alkyl radicals,

- (C_1-C_7)- alkylamino,

- di-(C_1 -C_7)-alkylamino,

- (C_1-C_6)-alkoxycarbonylamino,

- (C_7-C_{15})-aralkoxycarbonyl,

- (C_7-C_{15})-aralkoxycarbonylamino,

- phenyl-(C_1-C_4)-alkoxy

- 9-fluorenylmethoxycarbonylamino,

- (C_1-C_6)-alkylsulfonyl,

- (C_1-C_6)-alkylsulfinyl,
- (C_1-C_6)-alkylthio,
- hydroxamino,
- hydroximino,
- sulfamoyl,
- sulfo,
- carboxamido,
- formyl,
- hydrazono,
- imino,
- a radical $CONR^{12}R^{13}$ or $CONR^{12*}R^{13*}$,
- by up to six hydroxy or
- by up to five (C_1-C_8)-alkanoxyloxy;
- mono-, bi- or tri-cyclic (C_3-C_{18})-cycloalkyl,
- (C_3-C_{18})-cycloalkyl-(C_1-C_6)-alkyl, the cycloalkyl part in each case being substituted if appropriate by one or two identical or different radicals from the series
- F, Cl, Br, I,
- carboxy,
- carbamoyl,
- carboxymethoxy,
- hydroxy,
- (C_1-C_7)-alkoxy,
- (C_1-C_7)-alkyl,
- (C_1-C_7)-alkyloxycarbonyl,
- amino,

- (C_1-C_6)-alkylamino-(C_1-C_6)-alkyl,
- di-(C_1-C_6)-alkylamino-(C_1-C_6)-alkyl,
- amidino,
- hydroxamino,
- hydroximino,
- hydrazono,
- imino,
- guanidino,
- (C_1-C_6)-alkoxysulfonyl,
- (C_1-C_6)-alkoxysulfinyl,
- (C_1-C_6)-alkoxycarbonylamino
- (C_6-C_{12})-aryl-(C_1-C_4)-alkoxycarbonylamino,
- (C_1-C_7)-alkylamino,
- di-(C_1-C_7)-alkylamino and
- trifluoromethyl;
- (C_6-C_{14})-aryl,
- (C_6-C_{14})-aryl-(C_1-C_6)-alkyl,
- (C_6-C_{14})-aryloxy-(C_1-C_6)-alkyl or
- (C_6-C_{14})-aryl-(C_3-C_8)-cycloalkyl, wherein the aryl part in each case is substituted if appropriate by one, two or three identical or different radicals from the series
- F, Cl, Br, I,
- hydroxy,
- mono-, di- or tri-hydroxy-(C_1-C_4)-alkyl,
- trifluoromethyl,
- formyl,

- carboxamido,
- mono- or di-(C_1-C_4)-alkylaminocarbonyl,
- nitro,
- (C_1-C_7)-alkoxy,
- (C_1-C_7)-alkyl,
- (C_1-C_7)-alkoxycarbonyl,
- amino,
- (C_1-C_7)-alkylamino,
- di-(C_1-C_7)-alkylamino,
- carboxy,
- carboxymethoxy,
- amino-(C_1-C_7)-alkyl,
- (C_1-C_7)-alkylamino-(C_1-C_7)-alkyl,
- di-(C_1-C_7)-alkylamino-(C_1-C_7)-alkyl,
- (C_1-C_7)-alkoxycarbonylmethoxy,
- carbamoyl,
- sulfamoyl,
- (C_1-C_7)-alkoxysulfonyl,
- (C_1-C_8)-alkylsulfonyl,
- sulfo-(C_1-C_8)-alkyl
- guanidino (C_1-C_8)-alkyl and
- (C_1-C_6)-alkoxycarbonylamino;
- het,
- het-(C_1-C_6)-alkyl,
- het-(C_3-C_8)-cycloalkyl,
- het-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkyl,

- het-(C_3-C_8)-cycloalkoxy-(C_1-C_4)-alkyl,

- het-thio-(C_1-C_6)-alkyl,

- het-thio-(C_3-C_8)-cycloalkyl,

- het-thio-(C_3-C_8)-cycloalkyl-(C_1-C_4)-alkyl,

where in each case het stands for the radical of a 5- to 7-member monocyclic or 8- to 10-member bicyclic ring system which can be benzanellated, aromatic, partly hydrogenated or completely hydrogenated, which can contain as heteroelements one, two, three or four different radicals from the group N, O, S. NO, SO, SO_2, which can be substituted with 1 to 6 hydroxy and which, if appropriate, is mono-, di- or tri-substituted as defined for (C_6-C_{14})-aryl under a_1) and/or with oxo,

or mean a radical $NR^{12}R^{13}$ or $NR^{12*}R^{13*}$,

or

a_2)

- a radical of formula VIII or VIII*

R^{1a}-W (VIII)

R^{1a*}-W* (VIII*)

wherein R^{1a} and R^{1a*} are defined like R^1 and R^{1*} under a_1) and W and W* stand for -CO-, -CS-, O-CO-, $-SO_2-$, -SO-, -S-, $-NHSO_2-$, -NHCO-, -CH(OH)-, -N(OH)- or -CO-V- with V meaning a peptide with 1 to 10 amino acids;

or wherein R^1 and R^{1*}, independent of each other, together with R^{11} or R^{12} and the atoms that carry them form monocyclic or bicyclic, saturated or partly unsaturated ring systems with 5-12 ring members which in addition to carbon can also contain 1 sulfur atom, which may be oxidized to sulfoxide or sulfone;

a_3)

- a glycosyl radical, preferably a glucofuranosyl or glucopyranosyl radical, which is derived from naturally occurring aldotetroses, aldopentoses, aldohexoses, ketopentoses, ketohexoses, desoxyaldoses, aminoaldoses and oligosaccharides as well as their stereoisomers;

R^2 and R^{2*}

are defined independent of each other like R^1 and R^{1*} under a_1) or a_2) or together with R^4 or R^{4*} and the atoms carrying them form mono- or bicyclic, saturated or partly unsaturated ring systems with 5 to 12 ring members, or together with R^3 or R^{3*} and the atoms carrying them form cyclic, saturated or partly unsaturated ring systems with 3 to 12 ring members;

R^3 and R^{3*}

independent of each other mean

- hydrogen or
- $(C_1$-$C_3)$-alkyl;

R^4 and R^{4*},

independent of each other, mean

- hydrogen or
- $(C_1$-$C_8)$-alkyl;

R^5, R^{5*} and R^{5**},

independent of one another, mean

- hydrogen.
- hydroxy,
- amino or
- carboxy, or

with R^6, R^{6*} or R^{6**} together with the carbon atoms carrying these, in each case independent of one another, form a keto group;

R^6, R^{6*} and R^{6**},

independent of one another, mean

- hydrogen or
- (C_1-C_6)-alkyl or

in the case of l=0, R^6 and R^{6*} can possibly form a common bond;

R^7 means

- hydrogen,
- hydroxy or
- (C_1-C_6)-alkyl;

R^8 and R^{8*},

independent of each other, mean

- hydrogen or
- (C_1-C_8)-alkyl, or together with R^9 or R^{9*} and the atoms carrying these form mono- or bicyclic, saturated or partly unsaturated ring systems with 5 to 12 ring members;

R^9 and R^{9*}

independent of each other are defined like R^1 or R^{1*} under a_1), stand for hydroxy or (C_1-C_4)-alkanoyloxy, or together with R^{10} or R^{10*} and the atoms carrying these form cyclic, saturated or partly unsaturated ring systems with 3 to 12 ring members;

or

together with R^{11} or R^{11*} and the atoms carrying these form a mono- or bicyclic, saturated or partly unsaturated ring system with 5-12 ring members, which in addition to carbon can also contain 1 sulfur atom, which possibly can be

oxidized to sulfoxide or sulfone; or can contain 1 nitrogen atom, the ring system possibly being substituted by amino;

R^{10} and R^{10*},

independent of each other, mean

- hydrogen or
- (C_1-C_6)-alkyl;

R^{11} and R^{11*},

independent of each other, mean

- hydrogen,
- hydroxy,
- (C_1-C_4)-alkanoyloxy or
- (C_1-C_8)-alkyl;

R^{12}, R^{12*}, R^{13} and R^{13*},

independent of one another, mean

- hydrogen,
- (C_1-C_8)-alkyl which can be substituted by
- amino,
- (C_1-C_4)-alkylamino,
- di-(C_1-C_4)-alkylamino,
- mercapto,
- carboxy,
- hydroxy or
- (C_1-C_4)-alkoxy,
- (C_3-C_7)-cycloalkyl,
- (C_1-C_4)-alkoxycarbonyl,

- (C_6-C_{14})-aryl, - (C_6-C_{14})-aryl-(C_1-C_4)-alkoxycarbonyl which in the aryl part can be substituted as described for R^1 or R^{1*},

- het or

- het-(C_1-C_4)-alkyl, het being defined as described for R^1 or R^{1*},

or where R^{12} and R^{13} or R^{12*} and R^{13*} together with the nitrogen atoms carrying these form monocyclic or bicyclic, saturated, partly unsaturated or aromatic ring systems which in addition to carbon can also contain 1 or 2 nitrogen atoms, 1 sulfur atom or 1 oxygen atom as further ring members and which can be substituted by

(C_1-C_4)-alkyl,

where

in the compounds of formula I cited above, one or more amide groups (-CONH-) of the main chain can be replaced by $-CH_2NR^{14}-$, $-CH_2S-$, $-CH_2O-$, $-OCH_2-$, CH_2CH_2-, -CH=CH-(cis and trans), $-COCH_2-$, $-CH(OH)CH_2-$, $-CH_2SO-$, CH_2SO_2-, -COO-, $P(O)(OR^{15})CH_2-$ and $-P(O)(OR^{15})NH-$, or also by an amide group with reversed polarity (-HCHO-);

wherein R^{14} and R^{15},

independent of each other, stand for

- hydrogen or

- (C_1-C_4)-alkyl;

as well as their physiologically tolerated salts, characterized in that a fragment with terminal carboxyl group or its reactive derivative is coupled with a corresponding fragment with free amino group, possibly (a) temporarily introduced protective group(s) for the protection of other functional groups is split off, and the compound thus obtained is converted, if appropriate, into its physiologically tolerated salt.

2. Process for the production of a compound of formula I as contained in claim 1, characterized in that the radicals and symbols with and without asterisk are identical in each case.

3. Process for the production of a compound of formula I as contained in claims 1 and 2, characterized in that the compound is C_2-symmetrical.

4. Process for the production of a compound of formula I as contained in claims 1 to 3, characterized in that Y stands for a radical of formula II or a radical of formula III;

l, m, A, A*, D, D*, n, n*, o, o*, p and p* are defined as in claim 1;

E, E*, F, F*, G and G*, independent of each other, stand for a natural or unnatural α-amino acid or α-imino acid;

R^1 and R^{1*},

independent of each other, stand for

a_1) - hydrogen,

- carboxyl,

- (C_1-C_{16})-alkyl, which may be simply saturated and which may be substituted by up to 2 identical or different radicals from the series

- hydroxy,

- (C_1-C_4)-alkoxy,

- carbamoyl,

- (C_1-C_8)-alkanoyloxy,

- carboxy,

- (C_1-C_4)-alkoxycarbonyl,

- F,

- amino,

- (C_1-C_7)-alkylamino,

- di-(C_1-C_7)-alkylamino,
- (C_1-C_6)-alkoxycarbonylamino,
- benzyloxycarbonyl,
- benzyloxycarbonylamino,
- 9-fluorenylmethoxycarbonylamino,
- (C_1-C_4)-alkylsulfonyl,
- a radical $CONR^{12}R^{13}$ or $CONR^{12*}R^{13*}$,
- by up to six hydroxy or
- by up to four (C_1-C_8)-alkanoyloxy;
- mono- or bicyclic (C_3-C_{12})-cycloalkyl,
- (C_3-C_{12})-cycloalkyl-(C_1-C_6)-alkyl where in each case the cycloalkyl part is substituted by one or two identical or different radicals from the series
- F,
- carboxy,
- hydroxy,
- (C_1-C_7)-alkoxy,
- (C_1-C_4)-alkyl,
- (C_1-C_4)-alkyloxycarbonyl,
- amino,
- (C_1-C_6)-alkoxycarbonylamino,
- benzyloxycarbonylamino,
- (C_1-C_4)-alkylamino and
- di-(C_1-C_4)-alkylamino;
- (C_6-C_{10})-aryl,
- (C_6-C_{10})-aryloxy-(C_1-C_6)-alkyl or

- $(C_6$-$C_{10})$-aryl-$(C_1$-$C_6)$-alkyl, wherein the alkyl part in each case is possibly substituted by one, two or three identical or different radicals from the series

- F, Cl, Br,
- hydroxy,
- hydroxy-$(C_1$-$C_4)$-alkyl,
- carboxamido,
- mono- or di-$(C_1$-$C_4)$-alkylaminocarbonyl,
- $(C_1$-$C_4)$-alkoxy,
- $(C_1$-$C_4)$-alkyl,
- $(C_1$-$C_4)$-alkoxycarbonyl,
- amino,
- $(C_1$-$C_4)$-alkylamino,
- di-$(C_1$-$C_4)$-alkylamino,
- carboxy,
- carbamoyl,
- $(C_1$-$C_4)$-alkoxycarbonylamino;
- het,
- het-$(C_1$-$C_6)$-alkyl,
- het-$(C_5$-$C_6)$-cycloalkyl,
- het-thio-$(C_1$-$C_4)$-alkyl,
- het-thio-$(C_5$-$C_6)$-cycloalkyl,

where het in each case stands for a 5- to 6-member monocyclic or 8- to 10-member bicyclic ring system which can be aromatic, partly hydrogenated or completely hydrogenated, which can contain as heteroelements one, two, three of four different radicals from the group N, O, S, NO, SO, SO_2, which can be

substituted with 1 to 4 hydroxy and which can possibly be mono- or di-substituted as defined for (C_6-C_{10})-aryl under a_1) and/or with oxo,

or means a radical $NR^{12}R^{13}$ or $NR^{12*}R^{13*}$ or,

a_2) - a radical of formula VIII or VIII*

R^{1a} - W (VIII)

R^{1a*} - W* (VIII*)

wherein R^{1a} and R^{1a*} are defined like R^1 an R^{1*} under a_1) and W or W* stand for -CO-, -O-CO-, SO_2-, -SO-, -S-, -NHCO- OR -CH(OH)-;

or wherein R^1 and R^{1*} independent of each other together with R^{11} or R^{11*} and the atoms carrying these form monocyclic, saturated or partly unsaturated ring systems with 5-8 ring members, which in addition to carbon also can contain 1 sulfur atom, which can possibly be oxidized to sulfoxide or sulfone;

a_3) - a glycosyl radical that is defined as in claim 1;

R^2 and R^{2*},

independent of each other, mean

b_1) hydrogen,

- carboxy,

- (C_1-C_{10})-alkyl which is possibly simply or doubly unsaturated and which is possibly substituted by up to 3 identical or different radicals from the series

-hydroxy,

- (C_1-C_7)-alkoxy,

- (C_1-C_7)-alkylthio,

- (C_1-C_7)-alkylsulfinyl,

- (C_1-C_7)-alkylsulfonyl,

- (C_1-C_7)-alkanoyloxy,

- carboxy,
- (C_1-C_7)-alkoxycarbonyl,
- Cl, Br,
- amino,
- amidino,
- guanidino,
- N,N'-di-(benzyloxycarbonyl)-guanidino,
- Carbamoyl,
- (C_7-C_{15})-aralkoxycarbonyl,
- (C_1-C_5)-alkoxycarbonylamino,
- (C_7-C_{15})-aralkoxycarbonylamino or
- 9-fluorenylmethoxycarbonylamino;
- (C_3-C_{12})-cycloalkyl,
- (C_3-C_{12})-cycloalkyl-(C_1-C_3)-alkyl,
- (C_6-C_{14})-aryl,
- (C_6-C_{14})-aryl-(C_1-C_3)-alkyl, the aryl part in each case possibly being substituted by one, two or three identical or different radicals from the series
- F, Cl, Br, I,
- hydroxy,
- (C_1-C_7)-alkoxy,
- (C_1-C_7)-alkyl,
- (C_1-C_7)-alkoxycarbonyl,
- amino and
- trifluoromethyl; or

- het-(C_1-C_6)-alkyl, het standing for the radical of a 5- or 6-member monocyclic or 9- to 10-member bicyclic, possibly partly or completely hydrogenated heteroaromatic compound with at least 1 C atom, 1-4 N atoms and/or 1-2 S atoms and/or 1-2 O atoms as ring members, which is possibly mono- or di-substituted as described in claim 1 for the aryl part; or

b_2) together with R^4 or R^{4*} and the atoms carrying these form pyrrolidine or piperidine, which in each case can also be annelated, with cyclopentyl, cyclohexyl or phenyl,

or together with R^3 or R^{3*} and the atoms carrying these form cyclic, saturated or partly unsaturated ring systems with 3-8 ring members;

R^3 and R^{3*}

independent of each other mean

- hydrogen,
- methyl or
- ethyl;

R^4 and R^{4*}

independent of each other mean

- hydrogen,
- (C_1-C_4)-alkyl;

R^5, R^{5*} and R^{5**}

independent of each other are as defined in claim 1;

R^6, R^{6*} and R^{6**}

independent of one another mean

- hydrogen,
- (C_1-C_4)-alkyl;

R^7

means

- hydrogen,

- hydroxy or

- C_1-C_4)-alkyl;

R^8 and R^{8*}

independent of each other mean

- hydrogen,

- (C_1-C_8)-alkyl or together with R^9 or R^{9*} and the atoms carrying these form pyrrolidine or piperidine, which in each case can additionally be annelated with cyclopentyl, cyclohexyl or phenyl;

R^9 and R^{9*}

independent of each other are defined like R^2 or R^{2*} under b_1), or mean (C_1-C_8)-alkyl, or

together with R^{10} or R^{10*} and the atoms carrying these form a mono- or bicyclic, saturated or partly unsaturated ring system with 5-12 ring members;

or

together with R^{11} or R^{11*} and the atoms carrying these form a mono- or bicyclic, saturated or partly unsaturated ring system with 5-12 ring elements, which in addition to carbon can also contain 1 sulfur atom which can possibly be oxidized to sulfoxide or sulfone;

R^{10} and R^{10*}

independent of each other mean

- hydrogen or

- (C_1-C_4)-alkyl;

R^{11} and R^{11*}

independent of each other mean

- hydrogen,

- hydroxy,

- (C_1-C_4)-alkanoyloxy or

- (C_1-C_4)-alkyl;

R^{12}, R^{12*}, R^{13} and R^{13*}

independent of one another mean

- hydrogen,

- (C_1-C_8)-alkyl, which can be substituted by

- amino,

- (C_1-C_4)-alkylamino,

- di-(C_1-C_4)-alkylamino,

- carboxy,

- hydroxy or

- (C_1-C_4)-alkoxy,

- (C_1-C_4)-alkoxycarbonyl,

- (C_6-C_{10})-aryl, which can be substituted as described for R^1 or R^{1*},

- (C_6-C_{10})-aryl-(C_1-C_4)-alkoxycarbonyl,

- het or

- het-(C_1-C_4)-alkyl, het being defined as described for R^1 or R^{1*},

it being possible in the aforementioned compounds of formula I for one or more amide groups (-CONH-) of the main chain to be replaced by a group consisting of $-CH_2-NR^{14}-$, $-CH_2O-$, $-OCH_2-$, CH_2CH_2-, $-COCH_2-$, $-CH(OH)CH_2-$, -COO- or by an amide group of reverse polarity (-NHCO-);

R^{14} stands for

- hydrogen or

- (C_1-C_4)-alkyl;

as well as their physiologically tolerated salts.

5. Process for the production of a compound of formula I as described in claims 1 to 4, characterized in that

Y stands for a radical of formula II or a radical of formula III;

l, m, A, A*, D, D*, n, n*, o, o* are defined as in claim 1, p and p* stand for 1;

R^1 and R^{1*}

independent of each other stand for

- hydrogen,
- carboxyl,
- (C_1-C_{10})-alkyl,
- (C_3-C_8)-cycloalkyl,
- (C_3-C_8)-cycloalkyl-(C_1-C_{10})-alkyl,
- phenyl-(C_1-C_8)-alkyl, which in the phenyl part can be substituted as in claim 4,
- possibly protected mono- or di-amino-(C_1-C_{12})-alkyl or amino-(C_6-C_{10})-aryl-(C_1-C_4)- alkyl or amino-(C_3-C_{10})-cycloalkyl-(C_1-C_4)-alkyl, such as -2-amino-3-phenyl-propyl,
- mono-, di-, tris-, tetra-, penta- or hexahydroxy-(C_1-C_{10})-alkyl or -alkanoyl,
- (C_1-C_4)-alkoxy-(C_1-C_{10})-alkyl,
- (C_1-C_4)-alkoxycarbonyl-(C_1-C_{10})-alkyl,
- (C_1-C_{16})-alkylsulfonyl,
- (C_1-C_8)-alkylsulfinyl,
- mono-, di-, trihydroxy-(C_1-C_8)-alkylsulfonyl,
- mono-, di-, trihydroxy-(C_1-C_8)-alkylsulfinyl,
- mono-, di-, tri- or tetra-(C_1-C_8)-alkanoyloxy-(C_1-C_{10})-alkyl,

- (C_1-C_{14})-alkanoyl,
- possibly protected amino-(C_1-C_{11})-alkanoyl,
- di-(C_1-C_7)-alkylamino-(C_2-C_{11})-alkanoyl,
- (C_1-C_9)-cycloalkylcarbonyl,
- amino-substituted (C_3-C_9)-cycloalkylcarbonyl,
- amino-substituted (C_3-C_9)-cycloalkylsulfonyl,
- (C_6-C_{10})-aryl-(C_2-C_{11})-alkanoyl,
- (C_6-C_{10})-aryloxy-(C_2-C_{11})-alkanoyl,
- benzoyl, benzenesulfonyl or (C_6-C_{19})-aryl-(C_1-C_4)-alkylcarbonyl or -sulfonyl possibly substituted by amino, halogen, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxy or (C_1-C_7)-alkoxycarbonyl,
- (C_1-C_{10})-alkoxycarbonyl,
- substituted (C_1-C_{10})-alkoxycarbonyl
- (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl,
- (C_6-C_{10})-aryl-(C_1-C_8)-alkyl, (C_3-C_{10})-cycloalkyl-(C_1-C_8)-alkyl or (C_1-C_{10}) substituted by possibly protected amino and hydroxy,
- 9-flourenylmethoxycarbonyl,
- ketohexosyl,
- ketopentosyl,
- deoxyhexoketosyl,
- dexoypentoketosyl,
- aldohexosyl,
- aldopentosyl,
- deoxyhexoaldosyl,
- deoxypentoaldosyl,
- 2-amino-2-deoxyhexosyl

- 2-acetamido-2-dexoyhexosyl,

- lactosyl or

- maltosyl, it being possible for the joined sugar to be present in the pyranose or furanose form,

- het-(C_1-C_6)-alkyl,

- het-carbonyl or -sulfonyl,

- het-(C_1-C_6)-alkylcarbonyl or -sulfonyl,

- het-mercapto-(C_1-C_6)-alkylcarbonyl or -sulfonyl,

het in each case standing for

furyl, thienyl, benzothienyl, benzodioxolanyl, pyrrolyl, imidazolyl, isoxazolyl, thiazolyl, pyrazolyl, triazolyl, pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazinyl, pyrrolidyl, piperidyl, piperazinyl, morpholino, thiomorpholino, tetrahydrofuryl, tetrahydropyryl, tetrahydrothienyl, indolyl, quinolyl or isoquinolyl,

it also being possible for these to be substituted by one or two identical or different radicals from the group (C_1-C_4)-alkyl, (C_1-C_4)-alkoxy, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkoxycarbonylamino, hydroxy, amino, mono- or di-(C_1-C_4)-alkylamino and oxido;

R^2 and R^{2*}

independent of each other mean

- hydrogen,

- carboxyl,

- (C_1-C_8)-alkyl, which is possibly substituted by up to 2 identical or different radicals from the series

- hydroxy,

- (C_1-C_4)-alkoxy,

- (C_1-C_4)-alkylthio,
- (C_1-C_4)-alkylsulfinyl,
- (C_1-C_4)-alkylsulfonyl,
- (C_1-C_4)-alkanoyloxy,
- carboxy,
- (C_1-C_4)-alkoxycarbonyl,
- amino,
- amidino,
- guanidino,
- N,N'-di-(benzyloxycarbonyl)-guanidino,
- carbamoyl,
- (C_6-C_{10})-aryl-(C_1-C_3)-alkoxycarbonyl,
- (C_1-C_5)-alkoxycarbonylamino,
- (C_6-C_{10})-aryl-(C_1-C_3)-alkoxycarbonylamino, or
- (C_3-C_{10})-cycloalkyl,
- (C_3-C_{10})-cylcoalkyl-(C_1-C_3)-alkyl,
- (C_1-C_4)-(C_3-C_{10})-cylcoalkyl-(C_1-C_3)-alkyl,
- (C_6-C_{10})-aryl,
- (C_6-C_{10})-aryl-(C_1-C_3)-alkyl, the aryl part possibly being substituted by one, two or three identical or different radicals from the series
- F, Cl, Br,
-hydroxy,
- (C_1-C_4)-alkoxy,
- (C_1-C_4)-alkyl,
- (C_1-C_4)-alkoxycarbonyl and
- amino, or

- het-(C_1-C_4)-alkyl, het being defined as for R^1 or R^{1*},

R^3 and R^{3*}

independent of each other mean

- hydrogen or

- methyl,

R^4 and R^{4*}

independent of each other mean

- hydrogen or

- methyl,

R^5, R^{5*} and R^{5**}

independent of one another mean

- hydrogen,

- hydroxy,

- amino or

- carboxy;

R^6, R^{6*} and R^{6**}

independent of one another mean

- hydrogen or

- methyl;

R^7 means

- hydrogen,

- hydroxy or

- methyl;

R^8 and R^{8*}

independent of each other mean

- hydrogen,

- methyl, ethyl or n-propyl, or together with R^9 or R^{9*} and the atoms carrying these form a 1,2,3,4-tetrahydroisoquinoline or a 2-azabicyclooctane skeleton;

R^9 and R^{9*}

independent of each other are defined like R^2 and R^{2*} in claim 4, or mean (C_1-C_8)-alkanoyloxy or

together with R^{10} or R^{10*} and the atoms carrying these form cyclic ring systems with 5 to 7 ring members;

or together with R^{11} or R^{11*} form a form a thiochroman system the sulfur atom of which can if appropriate be oxidized to sulfone;

R^{10} and R^{10*}

independent of each other mean

- hydrogen or
- methyl;

R^{11} and R^{11*} are defined as in claim 4;

in the aforementioned compounds of formula I one or more amide groups (-CONH-) of the main chain can be replaced as defined in claim 4;

R^{14} stands for

- hydrogen or
- methyl;

as well as their physiologically tolerated salts.

6. Process for the production of a compound of formula I as contained in claims 1 to 5, characterized in that

R^1 and R^{1*}

independent of each other stand for

a_1) - hydrogen,

- carboxyl,

- (C_1-C_{16})-alkylsulfonyl
- (C_1-C_8)-alkylsulfinyl,
- (C_1-C_8)-mono-, di- or tri-hydroxyalkylsulfonyl,
- mono-, di-, tri- or tetra-hydroxy-(C_1-C_4)-alkyl,
- (C_1-C_8)-alkanoyloxy-(C_1-C_{10}) alkyl,
- 1,2-diacetoxyethyl,
- 1,2,3-triacetoxypropyl,
- (C_1-C_{14})-alkanoyl,
- amino-(C_1-C_{12})-alkanoyl,
- N-(C_1-C_4)-alkoxycarbonylamino-(C_1-C_8)-alkyl,
- di-(C_1-C_7)-alkylamino-(C_2-C_{11})-alkanoyl,
- (C_3-C_9)-cycloalkylcarbonyl,
- amino-(C_3-C_8)-cycloalkylcarbonyl,
- amino-(C_3-C_8)-cycloalkylsulfonyl,
- phenyl,
- (C_6-C_{10})-aryl-(C_2-C_{11})-alkanoyl,
- (C_6-C_{10})-aryloxy-(C_2-C_{11})-alkanoyl,
- benzoyl or benzenesylfonyl, possibly substituted by halogen, amino, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxy or (C_1-C_7)-alkoxycarbonyl,
- benzylsulfonyl, benzylsulfinyl or benzylthio, possibly substituted by halogen, amino, (C_1-C_7)-alkyl, (C_1-C_7)-alkoxy or (C_1-C_7)-alkoxycarbonyl,
- amino,
- (C_1-C_4)-alkoxycarbonylamino,
- (C_1-C_{12})-alkanoyl which is substituted by hydroxy, amino and possibly by phenyl or cyclohexyl,

- possibly protected, amino-substituted (C_6-C_{10})-aryl- or (C_3-C_{10})-alkyl or (C_1-C_8)-alkyl,

- (C_1-C_{10})-alkoxycarbonyl,

- substituted (C_1-C_{10})-alkoxycarbonyl,

- (C_6-C_{14})-aryl-(C_1-C_6)-alkoxycarbonyl,

- 9-fluorenylmethoxycarbonyl,

- 1-deoxyhexoketosyl or 1-deoxypentoketosyl,

- hexosyl or pentosyl

- 6-deoxyhexosyl,

- amino sugar radicals,

- lactosyl,

- maltosyl,

it being possible for the joined sugar to be present in the pyranose or furanose form,

- het,

- het-carbonyl or het-sulfonyl,

- het-(C_1-C_6)-alkyl,

- het-(C_1-C_6)-alkanoyl

- het-(C_1-C_6)-alkylsulfonyl or

- het-mercapto-(C_1-C_3)-alkylcarbonyl,

het standing in each case for

- pyrrolyl,

- imidazolyl,

- pyridyl,

- pyrimidyl,

- pyrrolidyl,

- piperidyl,

- morpholino,

- quinolyl or

- isoquinolyl,

and also possibly being substituted by one or two identical or different radicals from the group (C_1-C_4)-alkyl, (C_1-C_4)-alkoxycarbonyl, (C_1-C_4)-alkoxycarbonylamino, hydroxy, amino, mono- or di-(C_1-C_4)-alkylamino;

R^2 and R^{2*}

independent of each other stand for

- hydrogen,

- carboxyl,

- methyl, ethyl, isopropyl, n-propyl, n-butyl, isobutyl, sec.-butyl, n-pentyl, n-hexyl,

- cyclohexyl,

- cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl,

- 4-methylcyclohexylmethyl,

- 1-decahydronaphthylmethyl, 2-decahydronaphthylmethyl,

- phenyl,

- benzyl,

- 2-phenylethyl,

- 1-naphthylmethyl, 2-naphthylmethyl,

- 2-methylbenzyl, 3- methylbenzyl, 4-methylbenzyl,

- 2,4,6-trimethylbenzyl,

- 4-tert.-butylbenzyl,

- 4-tert.-butoxybenzyl

- 4-hydroxybenzyl,

- 4-methoxybenzyl,
- 2,4-dimethoxybenzyl,
- 3,4-dihydroxybenzyl,
- 3,4-dimethoxybenzyl,
- (benzodioxolane-5-yl)methyl,
- 4-chlorobenzyl,
- hydroxymethyl,
- 1-hydroxyethyl,
- 4-pyridyl,
- 4-(N-oxidopyridyl),
- 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-(4-pyridyl)-ethyl,
- 2-thienylmethyl, 3-thienylmethyl,
- 2-(2-thienyl)ethyl, 2-(3-thienyl)ethyl,
- indole-2-yl-methyl, indole-3-yl-methyl,
- (1-methyl-imidazole-4-yl)methyl,
- imidazole-4-yl-methyl, imidazole-1-yl-methyl,
- 2-thiazolylmethyl,
- 3-pyrazolylmethyl,
- 4-pyrimidylmethyl,
- 2-benzo[b]thienylmethyl, 3-benzo[b]thienylmethyl,
- 2-furylmethyl,
- 2-(methylthio)ethyl,
- 2-(methylsulfinyl)ethyl,
- 2-(methylsulfonyl)ethyl,

R^3, R^{3*}, R^4, R^{4*}, R^6, R^{6*}. R^{10} and R^{10*}

mean hydrogen;

R^5 and R^{5*}

independent of each other stand for

- hydrogen,
- hydroxy or
- amino;

R^7 means

- hydroxy or
- methyl;

R^8 and R^{8*}

independent of each other mean

- hydrogen or

together with R^9 or R^{9*} and the atoms carrying these form a 1,2,3,4-tetrahydroisoquinoline or 2-azabicyclooctane skeleton;

R^9 and R^{9*}

independent of each other are defined like R^2 or R^{2*} or mean

- hydroxy,
- acetoxy,
- tert.-butoxymethyl,
- 3-guanidinopropyl,
- carbamoylmethyl, carbamoylethyl,
- carboxymethyl, carboxyethyl,
- mercaptomethyl,
- (1-mercapto-1-methyl)ethyl,
- aminomethyl, 2-aminoethyl, 3-aminopropyl, 4-aminobutyl,
- N,N-dimethylamino,

- N,N'-di-(benzyloxycarbonyl)-guanidino-propyl,

- 2-benzyloxycarbonylethyl, benzyloxycarbonylmethyl,

- tert.-butylsulfonylmethyl

or

- 4-benzylcarbonylaminobutyl;

R^{11} and R^{11*}

independent of each other mean

- hydrogen,

- hydroxy or

- acetoxy,

and in the aforementioned compounds of this invention one or more amide groups (-CONH-) of the main chain can be replaced by $-CH_2NR^{14}-$ or $-CH(OH)CH_2-$;

R^{14} stands for

- hydrogen or

- methyl;

as well as their physiologically tolerated salts.

7. Process for the production of a compound of formula I as contained in claims 1 to 6, characterized in that

R^1 and R^{1*}

independent of each other stand for

$-a_1$) - hydrogen,

- carboxyl,

- (C_1-C_{16})-alkylsulfonyl,

- (C_1-C_8)-mono- or -dihydroxyalkylsulfonyl,

- mono-, di- or trihydroxy-(C_1-C_3)-alkyl,

- (C_1-C_8)-alkoxycarbonyl,

- (C_1-C_{14})-alkanoyl,
- amino-(C_1-C_{12})-alkanoyl,
- (C_6-C_{10})-aryl-(C_1-C_4)-alkylcarbonyl,
- 9-fluorenylmethoxycarbonyl,
- (C_1-C_4)-alkanoyloxy-(C_1-C_6)-alkyl,
- 1,2-diacetoxyethyl,
- 1,2,3-triacetoxypropyl,
- phenyl
- benzolsulfonyl possibly substituted by halogen, amino, (C_1-C_4)-alkyl or methoxy,
- benzolsulfonyl, -sulfinyl or - thio possibly substituted by halogen, amino, (C_1-C_4)-alkyl or methoxy,
- het or het-sulfonyl,
- het-(C_1-C_4)-alkanoyl,
- het-mercapto-(C_1-C_3)-alkylcarbonyl,

het in each case standing for

- pyrrolyl,
- imidazolyl,
- pyridyl,
- pyrimidyl,
- pyrrolidyl,
- quinolyl,
- isoquinolyl,
- piperidyl or
- morpholino,

it also being possible that this radical is substituted by one or two identical or different radicals from the group methyl, amino and (C_1-C_4)-alkoxycarbonylamino,

- amino-(C_3-C_6)-cycloalkylcarbonyl,
- (C_1-C_8)-alkanoyl, which is substituted by hydroxy and amino and possibly by phenyl or cyclohexyl,
- possibly protected amino-substituted phenyl- or cyclohexyl-(C_1-C_6)-alkyl,
- amino,
- (C_1-C_4)-alkoxycarbonylamino,
- benzyloxycarbonylamino,
- 1-deoxyhexoketosyl or 1-deoxypentoketosyl,
- hexosyl or pentosyl,

it being possible for the joined sugars to be present in the pyranose or the furanose form,

R^2 and R^{2*}

independent of each other stand for

- hydrogen,
- methyl, ethyl, isopropyl, n-propyl, n-butyl, isobutyl, sec.-butyl, pentyl, hexyl,
- cyclopentylmethyl, cyclohexylmethyl,
- 4-methylcyclohexylmethyl,
- benzyl,
- 2-phenylethyl,
- 1-naphthylmethyl, 2-naphthylmethyl,
- 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl,

- 2,4,6-trimethylbenzyl,

- 4-tert.-butylbenzyl,

- 4-methoxybenzyl,

- 3,4-dihydroxybenzyl,

- 2,4-dimethoxybenzyl,

- 3,4-dimethoxybenzyl,

- 3,4-dimethylenedioxylbenzyl,

- 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl or

- 2-(4-pyridyl)ethyl;

R^3, R^{3*}, R^4, R^{4*}, R^6, R^{6*}, R^7, R^{10} AND R^{10*}

mean hydrogen;

R^5 and R^{5*}

independent of each other mean

- hydrogen or

- hydroxy;

R^8 and r^{8*} independent of each other are defined as in claim 6,

R^9 and R^{9*}

independent of each other are defined like R^9 an R^{9*} in claim 6;

R^{11} and R^{11*} independent of each other are defined as in claim 6,

as well as their physiologically tolerated salts.

8. Process for the production of a compound of formula I as contained in claims 1 to 7, characterized in that

Y stands for a radical of formula III;

l means 0 or 1;

m means 1;

A, A^*, D and D^* are defined as in claim 1;

n, n*, o, o*, p and p* independent of one another mean 1;

E, E*, F, F*, G and G* independent of one another stand for an amino acid from the series Val, Lys, Lys(Z), Phe, Chg, Ser, Asn, Gly, Ile, Tbg, Nva or Npg;

R^1 and R^{1*} independent of each other mean

- hydrogen,
- carboxyl,
- methylsulfonyl,
- tert.-butylsulfonyl,
- tert.-butoxycarbonyl,
- 2-hydroxyethylsulfonyl,
- 1,2,3-trihydroxypropyl,
- 1,2,3-triacetoxypropyl,
- benzyloxycarbonyl,
- 4-methylphenylsulfonyl,
- 4-chlorobenzylthio,
- benzylsulfinyl,
- 4-chlorobenzylsulfonyl,
- hexadecylsulfonyl,
- 4-amino-1-piperidyl-sulfonyl,
- N-tert.-butoxycarbonyl-4-amino-1-piperidyl-sulfonyl,
- 4-amino-1-piperidyl-carbonyl,
- N-tert.-butoxycarbonyl-4-amino-1-piperidyl-carbonyl,
- 2-amino-3-phenyl-propyl,
- N-tert.-butoxycarbonyl-2-amino-3-phenyl-propyl,
- 2-amino-1-hydroxy-4-methyl-pentyl,
- deoxyfructos-1-yl,

- mannofuranosyl,
- 4-aminocyclohexylcarbonyl,
- 2-pyridylacetyl,
- 4-pyridylthio-acetyl,
- 2-quinolylcarbonyl,
- 1-naphthylacetyl,
- 1-naphthyloxyacetyl,
- 1-(4-pyridyl)-ethylsulfonyl,
- 12-aminododecanoyl,
- 4-(N-oxidopyridyl),
- 4-pyridyl,
- tetradecanoyl,
- phenyl,
- amino or
- tert.-butoxycarbonylamino;

R^2 and R^{2*} independent of each other mean

- hydrogen,
- 2-(4-pyridyl)ethyl,
- isopropyl,
- isobutyl,
- n-pentyl,
- benzyl,
- 3,4-methylenedioxybenzyl,
- 2,4-dimethoxybenzyl,
- 4-tert.-butylbenzyl,
- 2-phenylethyl or

- cyclohexylmethyl;

R^3, R^{3*}, R^4. R^{4*}, R^6, R^{6*}, R^7, R^{10} and R^{10*} mean

- hydrogen;

R^5 and R^{5*} independent of each other mean

- hydrogen or

- hydroxy;

R^8 and R^{8*} mean

- hydrogen, or together with R^9 or R^{9*} and the atoms carrying these form a 1,2,3,4-tetrahydroquinoline-3,4-diyl system;

R^9 and R^{9*} independent of each other mean

- hydrogen,
- hydroxy,
- acetoxy,
- n-propyl,
- isopropyl,
- isobutyl,
- aminomethyl,
- 4-aminobutyl,
- hydroxymethyl,
- tert.-butoxymethyl,
- aminocarbonylmethyl,
- 2-benzyloxycarbonyl-ethyl,
- 4-benzylcarbonylamino-butyl,
- N,N*-di(benzyloxycarbonyl)-guanidino-propyl,
- cyclohexyl,
- cyclohexylmethyl,

- benzyl,
- 2-phenyl-ethyl,
- 4-hydroxy-benzyl,
- 4-methoxy-benzyl,
- 4-tert.-butoxy-benzyl,
- 1-naphthylmethyl,
- 2-thienylmethyl,
- 1-imidazolyl-methyl,
- 3-indolyl-methyl,
- 4-pyridylmethyl,
- 4-(N-oxidopyridyl)methyl,
- 2-methylthio-ethyl,
- 2-methylsulfonyl-ethyl,
- tert.-butylsulfonyl-methyl or
- 2-carboxyl-ethyl;

R^{11} and R^{11*} independent of each other mean

- hydrogen
- hydroxy or
- acetoxy;

it being possible in the aforementioned compounds that one or more amide groups (-CONH-) of the main chain are replaced by $-CH_2NH-$ or $-CH(OH)CH_2-$; as well as their physiologically tolerated salts.

9. Process for the production of a compound of formula I as contained in claims 1 to 8, characterized in that

l = 0;

m = 1;

n + o + p = 1;

D and D* stand for a radical of formula VI or VI*;

R^1 and R^{1*} mean

- (C_1-C_{12})-alkylsulfonyl, which can possibly be substituted by up to 3 identical or different radicals from the series
- hydroxy,
- amino or
- carboxy;

R^2 and R^{2*} independent of each other mean

- hydrogen,
- carboxyl,
- methyl, ethyl, isopropyl, n-propyl, n-butyl, isobutyl, sec.-butyl, pentyl, hexyl,
- cyclohexyl,
- cyclopentylmethyl, cyclohexylmethyl, cycloheptylmethyl,
- 4-methylcyclohexylmethyl,
- 1-decahydronaphthylmethyl, 2-decahydroanaphthylmethyl,
- phenyl,
- benzyl,
- 2-phenylethyl,
- 1-naphthylmethyl, 2-naphthylmethyl,
- 2-methylbenzyl, 3-methylbenzyl, 4-methylbenzyl,
- 2,4,6-trimethylenzyl,
- 4-tert.-butylbenzyl,
- 4-tert.-butoxybenzyl,
- 4-hydroxybenzyl,

- 4-methoxybenzyl,
- 2,4-dimethoxybenzyl,
- 3,4-dihydroxybenzyl,
- 3,4-dimethoxybenzyl,
- (benzodioxolane-4-yl)methyl,
- 4-chlorobenzyl,
- hydroxymethyl,
- 1-hydroxyethyl,
- 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 2-(4-pyridyl)-ethyl,
- 2-thienylmethyl, 3-thienylmethyl,
- 2-(2-thienyl)ethyl, 2-(3-thienyl)ethyl,
- indole-2-yl-methyl, indole-3-yl-methyl,
- (1-methyl-imidazole-4-yl)methyl,
- imidazole-4-yl-methyl, imidazol-1-yl-methyl,
- 2-thiazolylmethyl,
- 3-pyrazolylmethyl,
- 4-pyrimidylmethyl,
- 2-benzo[b]thienylmethyl, 3-benzo[b]thienlymethyl,
- 2-furylmethyl,
- 2-(methylthio)ethyl,
- 2-(methylsulfinyl)ethyl or
- 2-(methylsulfonyl)ethyl;

R^3, R^{3*}, R^4, R^{4*}, R^6, R^{6*}, R^{11} an R^{11*} mean

- hydrogen;

R^5 and R^{5*} mean

- hydroxy;

R^9 and R^{9*}

are defined as in claim 8;

as well as their physiologically tolerated salts.

10. Process for the production of a pharmaceutical agent containing a compound of formula I as contained in claims 1 to 8, characterized in that it, and possibly one or more carriers, are brought into a form suitable for administering it.

11. Use of a compound of formula I as contained in claims 1 to 9 as a drug.

12. Use of a compound of formula I as contained in claims 1 to 9 for inhibiting retroviral proteases.

13. Use of a compound of formula I as contained in claims 1 to 9 in the treatment of "acquired immune deficiency syndrome."